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PATHO-PHYSIOLOGIC RESPONSE TO SINGLE AND MULTIPLE AIR POLLUTANTS IN HUMANS AND ANIMALS

Covering the Period
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By

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Graduate School of Public Health
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16. Abstracts Twenty healthy, adult male cats were lightly anesthetized (Nembutal), tracheotomized and were then breathed by a Harvard pump at a fixed frequency and tidal volume. Purified Medical Grade breathing air with or without sulfur dioxide in air or sulfur dioxide in combination with sodium chloride aerosol in air, was delivered to the animals in predetermined exposure sequences and for fixed durations of time. Parameters of response used to judge adaptation of cats to the inhaled challenges of pollutants were pulmonary flow resistance and lung compliance. Measurement methods were standard and included continuous trace recordings of air flow, tidal volume, transpulmonary pressure and blood pressure. Each animal acted as his own control. In addition, pollutant mixtures were delivered to animals via endotracheal catheter and/or face mask to evaluate the possible influence of receptors which may be present in the nasopharyngeal chamber and in the trachea above the tracheal cannula. After selected exposures, the pleural cavity was opened and liquid Freon was used to freeze the lungs. Procedures were developed to obtain histological sections in order to measure changes in airway size. The major finding was the variability of the responses of the test animals. Certain subjects showed increased pulmonary flow resistance at low SO2 concentration, and were the analogues of the "reactors" in human populations. Approximately 20 ppm SO2 in air were required to evoke a significant change in pulmonary flow resistance in "reactors". The majority of animals showed no response at this

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Pharynx
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concentration of sulfur dioxide in air, either alone or in the presence of NaCl aerosol (10 mg/m3). When the pollutants were administered via endotracheal catheter and face mask, an increased frequency of significant changes in pulmonary flow resistance in these animals was suggested, as compared to animals receiving challenges by tracheal cannula. However, fewer test animals were used in the former studies. All alterations in parameters of response were reversible shortly after exposure ceased. Morphological examination of lung tissue sections after rapid freezing with Freon indicated that measurement of alterations in airway size is not possible in the range of changes of pulmonary flow resistance reported here (< 100%). Methods and data for all experiments are presented in detail.

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SUMMARY

Twenty healthy, adult male cats were lightly anesthetized (Nembutal), tracheotomized and were then breathed by a Harvard pump at a fixed frequency and tidal volume. Purified Medical Grade breathing air with or without sulfur dioxide in air or sulfur dioxide in combination with sodium chloride aerosol in air, was delivered to the animals in predetermined exposure sequences and for fixed durations of time. Parameters of response used to judge adaptation of cats to the inhaled challenges of pollutants were pulmonary flow resistance and lung compliance. Measurement methods were standard and included continuous trace recordings of air flow, tidal volume, transpulmonary pressure and blood pressure. Each animal acted as his own control. In addition, pollutant mixtures were delivered to animals via endotracheal catheter and/or face mask to evaluate the possible influence of receptors which may be present in the nasopharyngeal chamber and in the trachea above the tracheal cannula. After selected exposures, the pleural cavity was opened and liquid Freon was used to freeze the lungs. Procedures were developed to obtain histological sections in order to measure changes in airway size.

The major finding of the study was the variability of the responses of the test animals. Certain subjects showed increased pulmonary flow resistance at low SO_2 concentration, and were the

analogues of the "reactors" in human populations. Approximately 20 ppm SO_2 in air were required to evoke a significant change in pulmonary flow resistance in "reactors". The majority of animals showed no response at this concentration of sulfur dioxide in air, either alone or in the presence of NaCl aerosol (10 mg/m^3). When the pollutants were administered via endotracheal catheter and face mask, an increased frequency of significant changes in pulmonary flow resistance in these animals was suggested, as compared to animals receiving challenges by tracheal cannula. However, fewer test animals were used in the former studies.

All alterations in parameters of response were reversible shortly after exposure ceased. This finding in cats is similar to reports of early reversal of these parameters in spontaneously breathing human subjects exposed to the same pollutants. In guinea pigs, pulmonary flow resistance, which was elevated by exposure to pollutants, returned to normal after a prolonged period (at least one hour) following cessation of exposure.

Morphological examination of lung tissue sections after rapid freezing with Freon indicated that measurement of alterations in airway size is not possible in the range of changes of pulmonary flow resistance reported here (< 100%).

Methods and data for all experiments are presented in detail.

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I. INTRODUCTION

A. Review of Contract Aims and Efforts

This Contract was initiated on January 3, 1967. Its aim was to perform a series of experiments in animals and in man to determine the extent of and the mechanisms associated with, synergism between inert aerosols and irritant gas in combination after inhalation. The parameters used to judge synergistic response were to be changes in pulmonary mechanics. Initially, it was our aim to study humans in both the resting state and during exercise. The departure from this laboratory of Dr. George Burton for Loma Linda University in 1968 resulted in curtailment of human studies because a physician was not associated with the study, thus precluding adherence to University guidelines for experiments involving human subjects. However, studies involving exposures of human subjects at rest were completed and a publication entitled "Response of Healthy Men to Inhaled Low Concentrations of Gas-Aerosol Mixtures" by Burton, G., Corn, M., Gee, B. L., Vasallo, C. and Thomas, A. P. resulted and appeared in the AMA Archives of Environmental Health 18, 681 (1969). (Appendix I.) Efforts on this Contract then shifted to studies of synergism in cats exposed to the same aerosol-irritant gas mixture as was used in the human studies. In addition to the presence or absence of response, we were interested in the mechanisms associated with the response.

Quarterly Progress Reports have been submitted since the inception of this Contract. The publication referenced above summarized the work accomplished during the initial 18 months of the

Contract. The purpose of this report is to summarize efforts during the latter 18 months of the investigation. Progress during this period was exclusively associated with synergistic studies utilizing cats as test animals. The work reported here is scheduled for presentation at the 10th Air Pollution Medical Research Conference to be held in New Orleans, October 5-7, 1970. The paper is entitled "Response of Cats to Inhaled SO_2 and SO_2-NaCl Aerosol Mixtures in Air" by M. Corn, N. Kotsko, D. Stanton, and W. Bell. The presentation will be a summary version of data and discussion presented here.

B. Background for Inhalation Studies Using Cats as Subjects

The biological assay procedure for air pollutants, as originally developed by Amdur and Mead(1), utilizes guinea pigs as experimental animals. The results of work by Amdur and her coworkers is reviewed in the document Air Quality Criteria for Sulfur Oxides(2). The more than a decade of work by Amdur, in which guinea pigs have been exposed to a variety of gaseous and particulate pollutants, provides the most extensive body of information available on the response of an animal species to air pollutants. The data relative to human response to mixtures of pollutants, as judged by alterations in parameters of pulmonary mechanics, have not substantiated the findings in guinea pigs. The studies on humans are few in number and are contradictory, as discussed by Amdur in a recent appraisal of sulfur dioxide-aerosol mixtures and their effects on animals and man(3). Because of heavy reliance on the guinea pig assay system and the difficulties inherent in extrapolating these data to man, or even in drawing conclusions from these data relative to effects of these systems on man, it was considered appropriate to study the effects of these mixtures on another species.

A reasonable and appropriate question is "why select the cat as the species of choice in these studies?" A series of investigations by Widdicombe(4,5,6) and Nadel(7,8) delineated the mechanisms of bronchoconstriction and peripheral airway constriction in cats. Thus, studies of response to pollutant gas and aerosol mixtures in cats promised to answer whether the responses reported in guinea pigs occurred in other animal species. Also, if they occurred, the mechanisms of action could be investigated by isolating previously studied mechanisms and pathways of response by means of well developed experimental techniques. The investigation reported herewas a follow-up to this reasoning. We report on the effects of sulfur dioxide alone, and in combination with sodium chloride aerosol, on the pulmonary flow resistance and lung compliance of cats. In addition, results will be reported for pathological examination of lungs initially rapidly frozen with liquid Freon following exposure to pollutant free or to pollutant laden air. Experimental methods will be described and this will be followed by results and discussion.

II. EXPERIMENTAL METHODS

A. Pollutant Aerosol and Gas Concentration

Pollutant mixtures for the exposures were produced using a portable aerosol and pollutant gas supply apparatus designed and constructed for this study (Fig. 1).

Medical-grade compressed air was passed through activated carbon and silica gel. The stream of air was metered by the use of calibrated orifices, before entering the Dautrebande $D_{30}l$ generator or the Venturi tube for mixing with aerosol and gas. Sulfur dioxide gas was supplied to the Venturi throat by a syringe driven by an infusion pump. The Dautrebande $D_{30}l$ aerosol generator was filled with isotonic NaCl and placed in an opening at the base of the Venturi tube. The salt solution was replaced every 15 minutes to prevent a significant increase in NaCl concentration due to the evaporation of water.

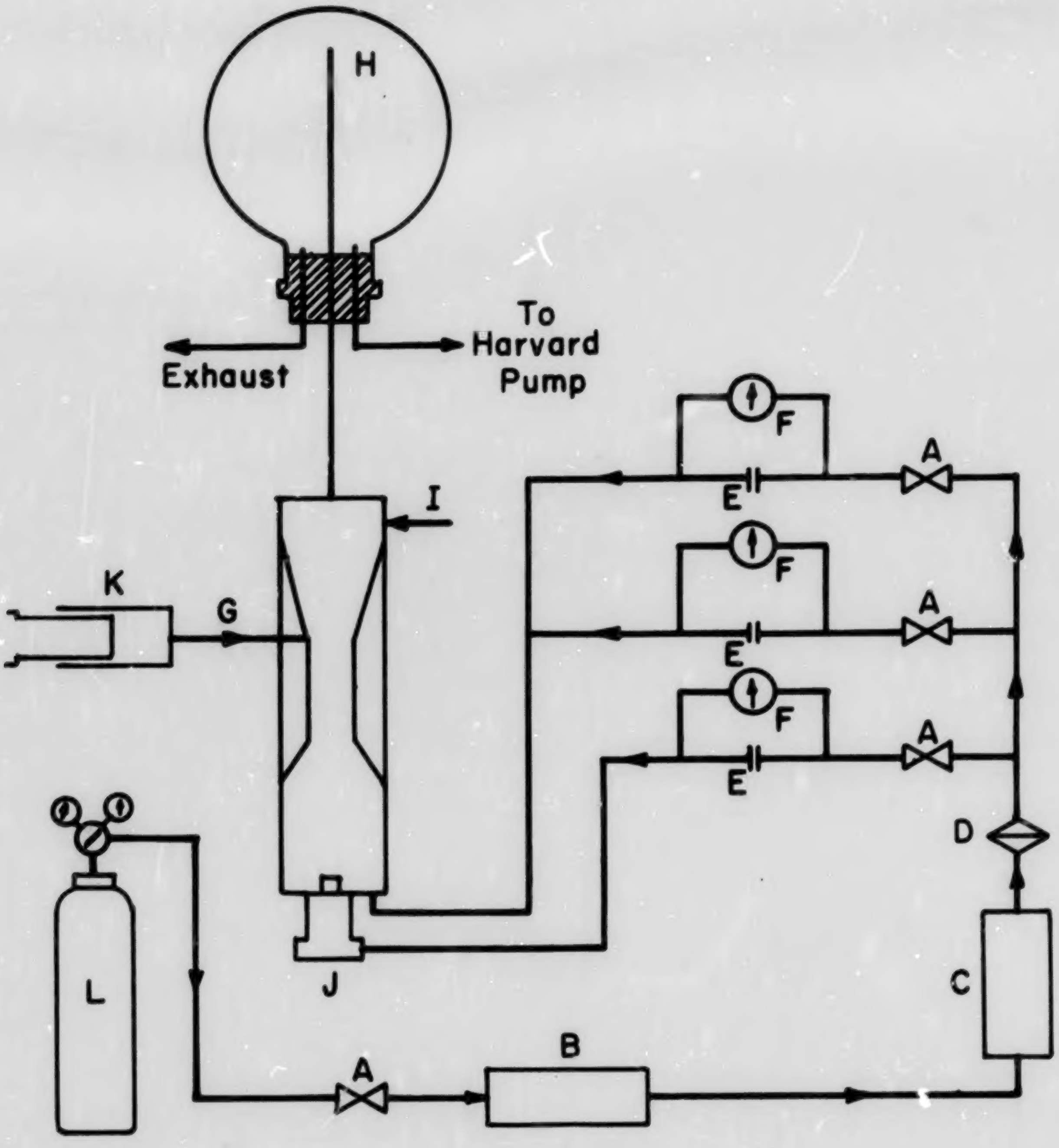
The mixture exited from the Venturi mixing tube into a reservoir balloon, where it was either exhausted, or withdrawn by the Harvard pump.

All components of the system, with the exception of the balloon, were of stainless steel, rigid plastic, or Teflon.

A three way valve at the entry to the Harvard pump could be set for pollutant mixture or room air entry to the pump. The Harvard pump was equipped to permit the setting of tidal volume and breathing frequency. The most commonly used settings for these parameters were 75 ml and 20 cps, respectively. The inspiratory stroke of the pump was under positive pressure. The animal expired under the driving force of lung elasticity.

FIGURE 1

SCHEMATIC OF POLLUTANT GENERATION APPARATUS


H
To
Harvard
Pump
Exhaust
F
A
E
I
F
K
G
A
E
F
A
E
D
J
C
L
B
A

Schematic of pollutant generation apparatus. A, Valves; B, "catch-all" air cleaner; C, silica gel; D, Millipore HA filter; E, Critical orifice; F, pressure gauge; G, SO_2 inlet; H, mixing balloon; I, Herschel-Type Venturi tube; J, Dautrebande D30l; K, Motor driven syringe; L, Medical grade compressed air; triangle, flow direction.

B. Pollutant Gas and Aerosol Sampling and Analysis

Samples for measurements of aerosol and pollutant gas concentrations were withdrawn from a stainless steel port in the exhaust line following the balloon reservoir. It was ascertained that concentrations measured above the tracheal cannula did not differ from those withdrawn at the former site.

1. Sulfur Dioxide

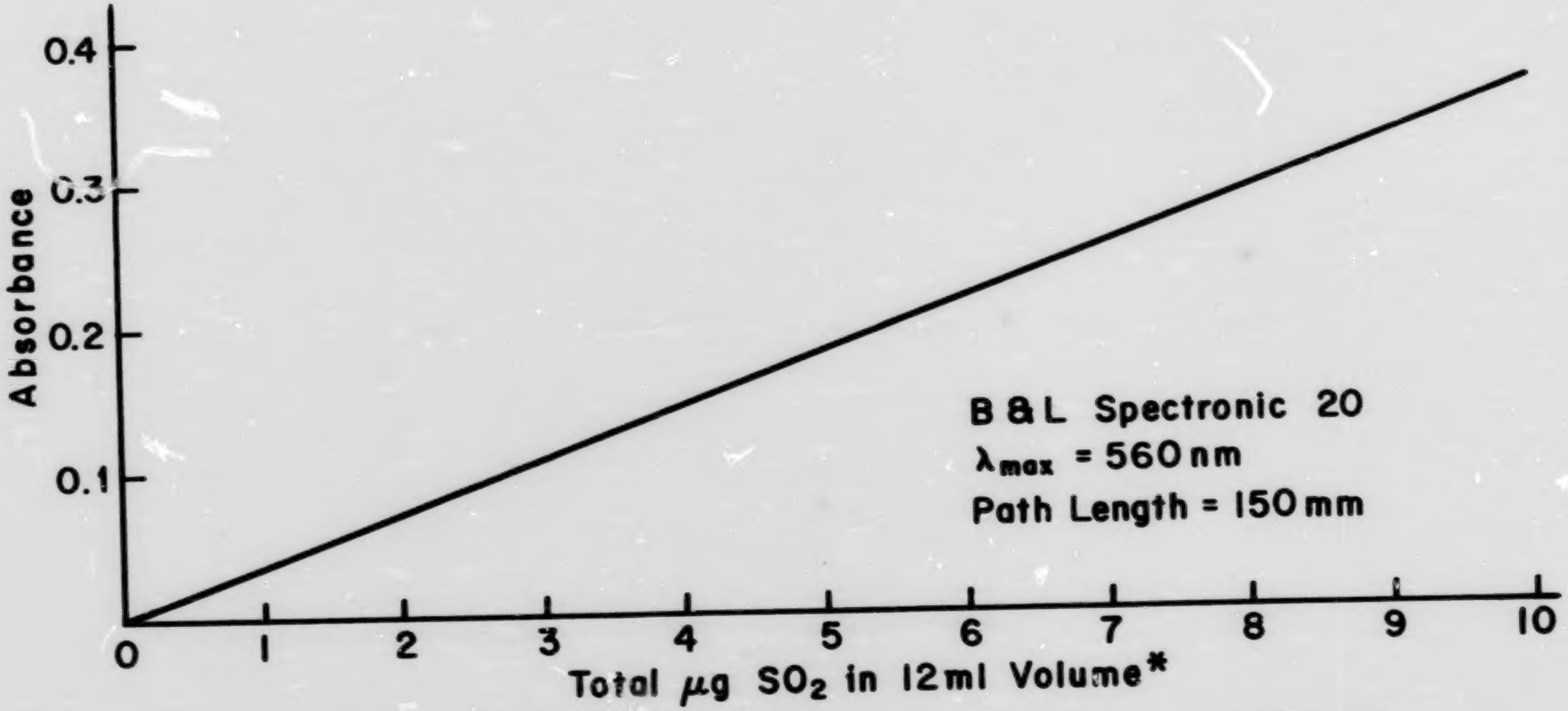
In order to determine SO_2 concentration, 0.76 liters/ min. of the pollutant mixture was drawn for three minutes into a midget impinger containing 10 ml of West-Gaeke reagent. The samples were then analyzed spectrophotometrically using the West-Gaeke method(9) with the Pararosaniline modification specified by Pate(10). The high sulfur dioxide concentrations in the experimental protocol required additional modifications in the analytical method, as follows.

a) A 1 ml aliquot was removed from the original 10 ml sample and was diluted with 10 ml of unexposed absorbing reagent. The 9 ml and 1 ml aliquots were then prepared according to the original West-Gaeke procedure(9).

b) A calibration curve was prepared using standardized solutions of sodium bisulfite, which ranged in concentration from 0.1 to 5.0 μg of SO_2 per ml. The solutions were standardized by the iodometric titration method described by the Intersociety Committee for Ambient Air Sampling and Analysis(11). A new calibration curve was prepared whenever a new stock dye solution was used. A typical calibration curve is shown in Figure 2. All calibration

FIGURE 2

CALIBRATION CURVE FOR SO_2 USING MODIFIED
WEST-GAEKE PROCEDURE



* 12 ml includes 10 ml. absorbing reagent + 1 ml dye + 1 ml formaldehyde

CALIBRATION CURVE FOR
THE DETERMINATION OF
SULFUR DIOXIDE USING
THE WEST-GAEKE METHOD

curves adhered to Beer's Law in the absorbance range less than 0.700. If a 9 ml sample yielded an absorbance value greater than 0.700, it was discarded and the 1 ml sample was analyzed.

The concentration of SO_2 in μg SO_2 per ml was calculated as follows:

$$\mu g\ SO_2 \text{ per ml} = \frac{V_T \times \text{Absorbance}}{\text{Slope} \times V_F}$$

where V_T = total volume of solution, ml

V_F = fraction of original sample analyzed

The total volume of the 9 ml sample was 11 ml, which consisted of 9 ml of the original sample, 1 ml of dye and 1 ml of formaldehyde. The 1 ml sample contained a total volume of 13 ml, which consisted of 1 ml of the original sample, 10 ml of unexposed absorbing reagent, 1 ml of dye and 1 ml of formaldehyde.

The concentration of sulfur dioxide was converted to Parts Per Million (ppm) in air as follows:

$$\text{PPM } SO_2 = \frac{382 \times C}{R \times T}$$

where 382 = Conversion factor for μg/ml to ppm at 25°C, 760 mm.

C = Concentration of SO_2 in μg/ml

R = Sample flow rate in cc per minute

T = Sample time in minutes

It should be noted that whenever sodium chloride was present in the system, sampling for sulfur dioxide was performed by first drawing a sample through HA Millipore filter paper to eliminate sodium chloride interference. Several calibration runs indicated that the loss of sulfur dioxide on the filter paper was negligible.

2. Sodium Chloride Aerosol

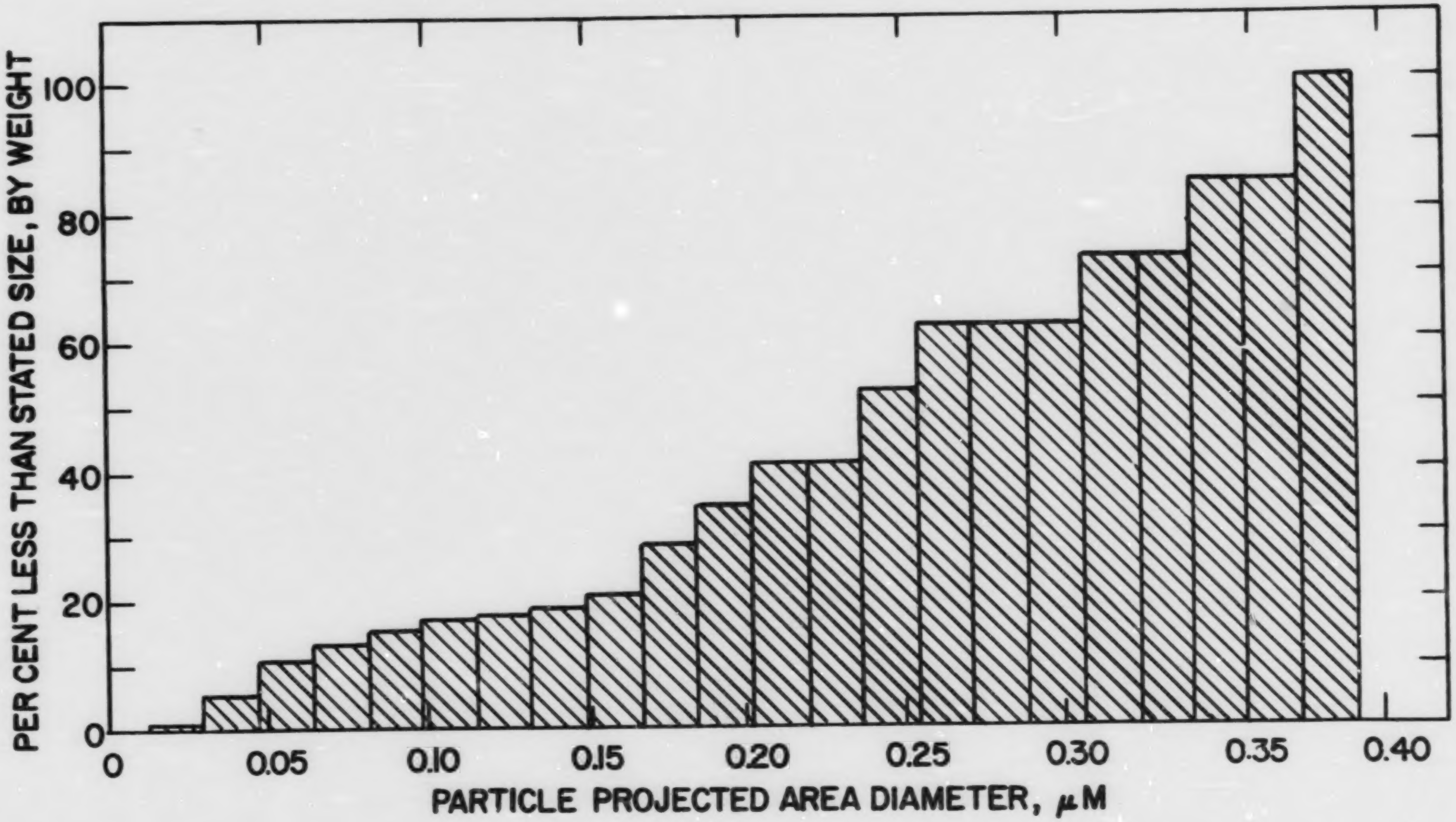
The concentration of sodium chloride aerosol was determined by withdrawing the exposure mixture at 21 liters/min. for 20 minutes through HA Millipore paper, leaching the salt by filter immersion in distilled water, and analyzing electrical conductivity. A calibration curve was prepared using reagent-grade sodium chloride. Because of the length of time required to sample for the sodium chloride aerosol, this was done at the end of the exposure periods. Several nonexposure and postexposure checks found the concentrations to be very consistent over a period of several hours.

The particle size distribution of the aerosol was determined by first sampling with an oscillating thermal precipitator onto a carbon-coated glass coverslip. The carbon film was transferred to a 200 mesh electron microscope grid prior to obtaining photographs with an electron microscope. The particles were sized using a Zeiss TGZ3 particle sizing unit. The particles were all smaller than 0.40 µm by weight; the mean size and standard deviation were 0.25 µm and ± 0.01 µm, respectively. (Figure 3.)

The concentrations of SO_2 gas and NaCl aerosols used in these studies will be cited in the Results and Discussion section of this report. However, it is appropriate here to indicate the variations in concentrations used in these studies. LOW sulfur dioxide concentrations were 15-25 ppm. HIGH sulfur dioxide concentrations were 30-40 ppm. Sodium chloride aerosol concentrations were 9-10 mg/m^3.

FIGURE 3

CUMULATIVE PARTICLE SIZE DISTRIBUTION CURVE FOR TEST AEROSOL SIZED AT 32,000x



CUMULATIVE PARTICLE-SIZE DISTRIBUTION
CURVE FOR TEST AEROSOLS (NaCl),
SIZED AT 32,000x WITH ZEISS
TGZ-3 AND ELECTRON MICROSCOPE

A representative time-concentration diagram for each pollutant during a single experiment is shown in Figure 4 (Cat No. 1610).

C. Animal Handling and Preparation

Upon receipt of animals a routine examination was made to determine the presence of gross abnormalities. Animals with abnormalities were returned to the supplier; all other animals were weighed and were then injected with feline pneumonitis vaccine. (Veterinary care or consultation was available when needed.) An initial isolation period of 2 weeks was observed.

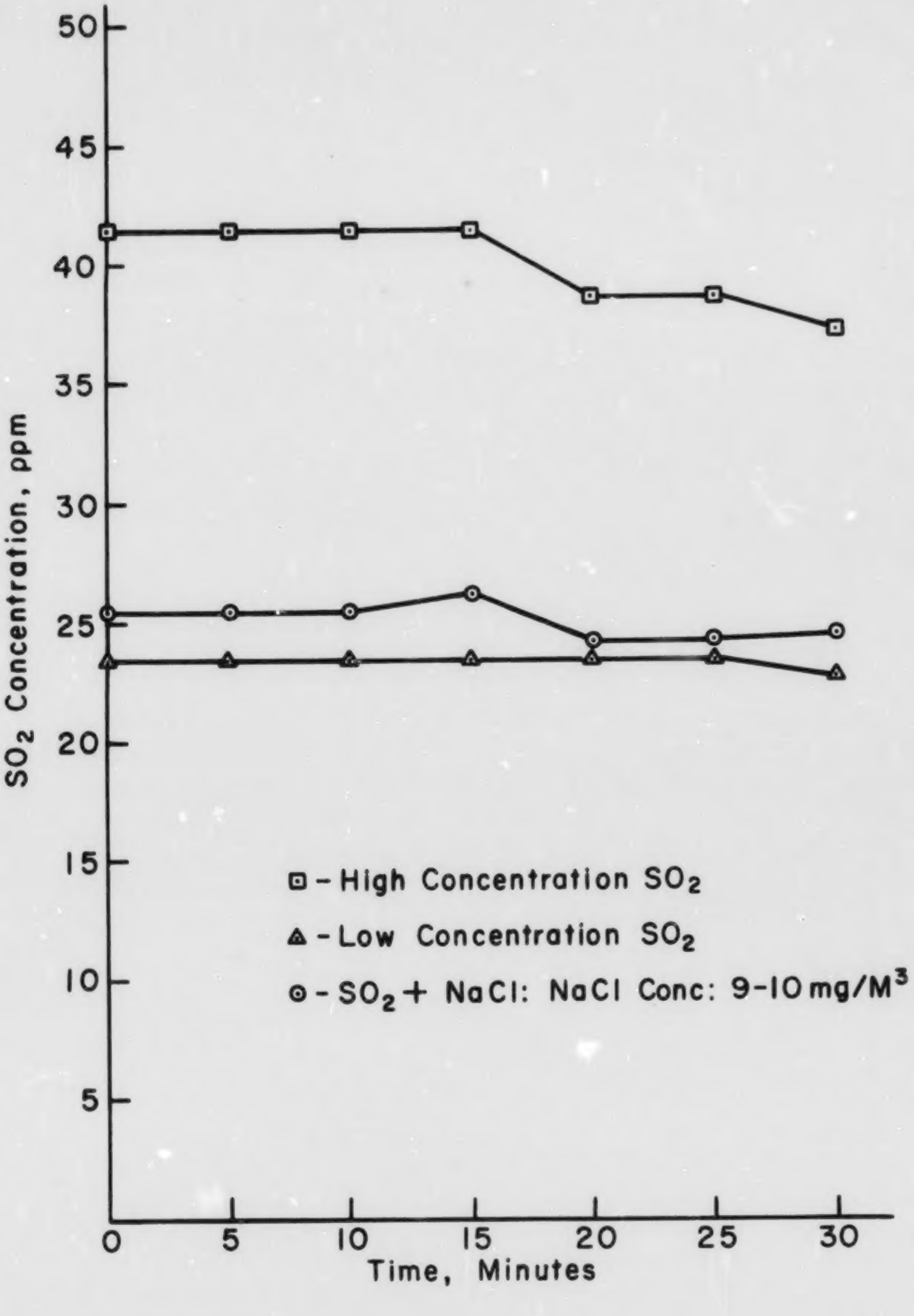
All animals were caged, fed, and attended in accordance with the rules and regulations of the United States Department of Agriculture and Federal Act of August 24, 1966 (P.L. 89-544). A trained technician observed, weighed and kept a daily record of any changes that occurred. At the conclusion of the isolation period animals were permitted to exercise daily.

Food and water were removed from an animal cage 18 hours prior to inhalation exposure. An examination was performed for symptoms of diarrhea, diuresis, conjunctivitis, etc. The entire ventral and cervical region of the cat was then shaved and a vacuum was used to remove excess hair.

Nembutal (30 mg/Kg, intraperitoneally) was used to anesthetize adult cats weighing 2-5 Kg. Occasionally additional nembutal was required. We preferred to keep the cats in a light surgical anesthesia (Stage III). A check of the pedal and corneal reflexes were made to determine if additional nembutal was required. The booster dose, if required, was given intravenously in diluted

FIGURE 4

TYPICAL VARIATIONS IN POLLUTANT CONCENTRATIONS
DURING AN EXPERIMENT



TYPICAL SYSTEM PERFORMANCE: SO_2 EXPOSURE CONCENTRATION VS. TIME saline solution. When an animal did not relax, Gallamine Triethiodide, a muscle relaxant, was administered. It produces a nondepolarization block at the neuromuscular junction. The dosage was 0.05 mg/Kg, intravenously.

Two surgical procedures were used. In the first method, a tracheotomy was performed by using a Bard Parker #3 holder with #15 rib back blade. A 1 inch incision was made approximately 20 mm below the larynx in the center of the ventral region of the throat. The muscle was separated by using two small hemostats which were spread in opposite directions until the trachea was visible. A slightly larger hemostat was inserted under the trachea and was then lifted on the opposite side, where at this time a 6" length of suture was attached. This hemostat was left in position. A small horizontal cut was made between the cartilage rings of the trachea and a suitable size cannula was inserted. The cannulas which were used were 6.35 mm i.d. and 7.98 mm i.d. with 7/16" diameter side air tube. The hemostat was withdrawn after bringing 3" of the suture to the opposite side of the trachea and tying the cannula to hold it intact. In vagotomized cats we tied off the vagus nerve before inserting the cannula. The side air tube of the cannula was connected to a Fleisch Pneumotachograph (0), which in turn was connected to a Model #607 Harvard Animal Breathing Pump.

The second method utilized similar procedures, but in this case an endotracheal tube was placed at the entrance of the larynx. The epiglottis was sighted with the aid of a laryngscope and was then held open by a small hemostat. A #16 Foregger endotracheal tube (i.d. 2.5 mm, o.d. 5.3 mm), previously interlined with Teflon and having a built-in cuff, was then placed into the mouth of the larynx and the hemostat was released from the epiglottis. The cuff was inflated, clamped with a hemostat, and the tube was connected to the air pump in the usual manner. Whenever excessive mucus was found, suction was used to remove it.

A third and final preparation was used where a tracheotomy was initially performed, as described in the first method. A second cannula (same size) was inserted to provide a pathway to the nasopharyngeal chamber of the animal. The side air tube of the cannula was connected to an exhaust outlet. A face mask made of Lucite and anatomically sculptured for perfect fit was placed on the animal's face and was held in place with adhesive tape. The Teflon tubing nipple of the mask was connected to a small pump for flushing.

Preparation for intrapleural catheter insertion was initiated by a 5 mm incision in the right lateral thoracic region between the fourth and fifth rib. We used two small hemostats to probe and spread in opposite directions until we entered the intrapleural space. The hemostat was held in position immediately upon entry into the thoracic cavity. A #10 Malecot intrapleural catheter (.089" i.d.) was clamped onto the second hemostat and in a concerted movement one hemostat was withdrawn and the other, with the attached catheter, was inserted. The incision was sealed with wound clips. The catheter was connected to the side arm of a Statham differential strain gauge (Transducer Model No. PM 5 ± 0.2-350). The other arm of the strain gauge was connected to an opening on the side of the tracheal cannula.

In order to record blood pressure, intramedic polyethylene tubing (.045" i.d.) was inserted into the femoral artery and was then connected to a Statham strain gauge (Model No. P23Db series pressure transducer). The pressure dome of the transducer was filled with 1/200 solution of heparin and sodium chloride. The same size catheter was inserted into the femoral vein for administering drugs. Blood loss from surgery was minimal.

At the conclusion of inhalation exposures, the cat was sacrificed by administering an additional dose of nembutal. The thorax was opened by making a midline incision in the ventral thoracic region. The muscle was separated, costal cartilage dissected, sternum and eight pairs of ribs were removed. Portions of all lung lobes were exposed. We applied a modified Staub freeze technique(12) using Freon 12 (Dichlorodifluoromethane). Freon 12 was chosen because it was not hazardous, it required no extensive preparations for use, and good frozen sections were obtained.

D. Determination of Pulmonary Flow Resistance and Lung Compliance

The surgical preparations described above were followed by the hook-up of Statham transducers to the Electronics for Medicine Model DR-8 amplifiers for oscilloscope readout. The signals monitored and their respective transducers are shown in Table 1.

The signals from the DR-8 amplifiers or integrators could be visually read on an integral oscilloscope or recorded on LW-27, 18 cm photographic paper. A second oscilloscope provided visual display of R_L and C_L loops. These could also be permanently recorded on the photographic paper. Dry records were obtained in four seconds by means of a Rapid Writer attachment.

TABLE 1

PARAMETERS RECORDED ON THE ELECTRONICS FOR MEDICINE UNIT AND ASSOCIATED TRANSDUCERS

Parameter	Transducer	Pressure Range
Intrapleural Pressure (TPP)	Statham Model No. PM 5 ± 0.2-350 Serial No. 12394	± 0.2 psid
Air Flow ($\dot{V}$)	Fleisch Pneumotachograph with Statham Model No. PM 283TC ± 0.15-350	± 0.15 psid
Volume of Air (V)	Signal from $\dot{V}$ is electronically integrated	
Blood Pressure	Statham Model No. P23Db. Serial No. 11680	

Representative sweep and loop tracings from the Rapid Writer are shown in Figure 5.

Figure 6 is a photograph which shows the test cat connected to the Harvard Pump and the pneumotachograph in position.

In these studies animals were ventilated at 50-80 cc per stroke at a frequency of 18-21 strokes per minute. Thus, on the basis of an average tidal volume of 26 cc for the cat, these animals were hyperventilated.

When using oscilloscope loops, the total lung resistance was measured by subtracting a voltage proportional to lung volume change (and this proportional to compliance pressure) from the pressure axis of a pressure flow trace recorded on the oscilloscope screen(13). The voltage subtracted was sufficient to close the loop. The slope of the line resulting from closing the loop represented total lung resistance, which includes airway resistance and the viscous resistance of the lung tissue.

Calibration of all transducers was performed at the completion of each experiment. The correspondence between water or mercury manometers as primary standards and the LW-27 photographic paper readout of BP and TPP was recorded. Air Flow ($\dot{V}$) was calibrated by utilizing compressed air and a rotameter calibrated against a wet test meter. Volume was calibrated by alternately depressing or withdrawing the barrels of two opposed 100 ml syringes in a closed air loop with the Fleisch Pneumotachograph; 20 ml increments of volume yielded a step function on the record chart. Loop signals were calibrated in a similar manner, except that signal deflections were measured directly on the oscilloscope face.

FIGURE 5

REPRESENTATIVE SWEEP AND LOOP TRACINGS USING E FOR M RAPID WRITER AND LW-27, 18 cm PHOTOGRAPHIC PAPER

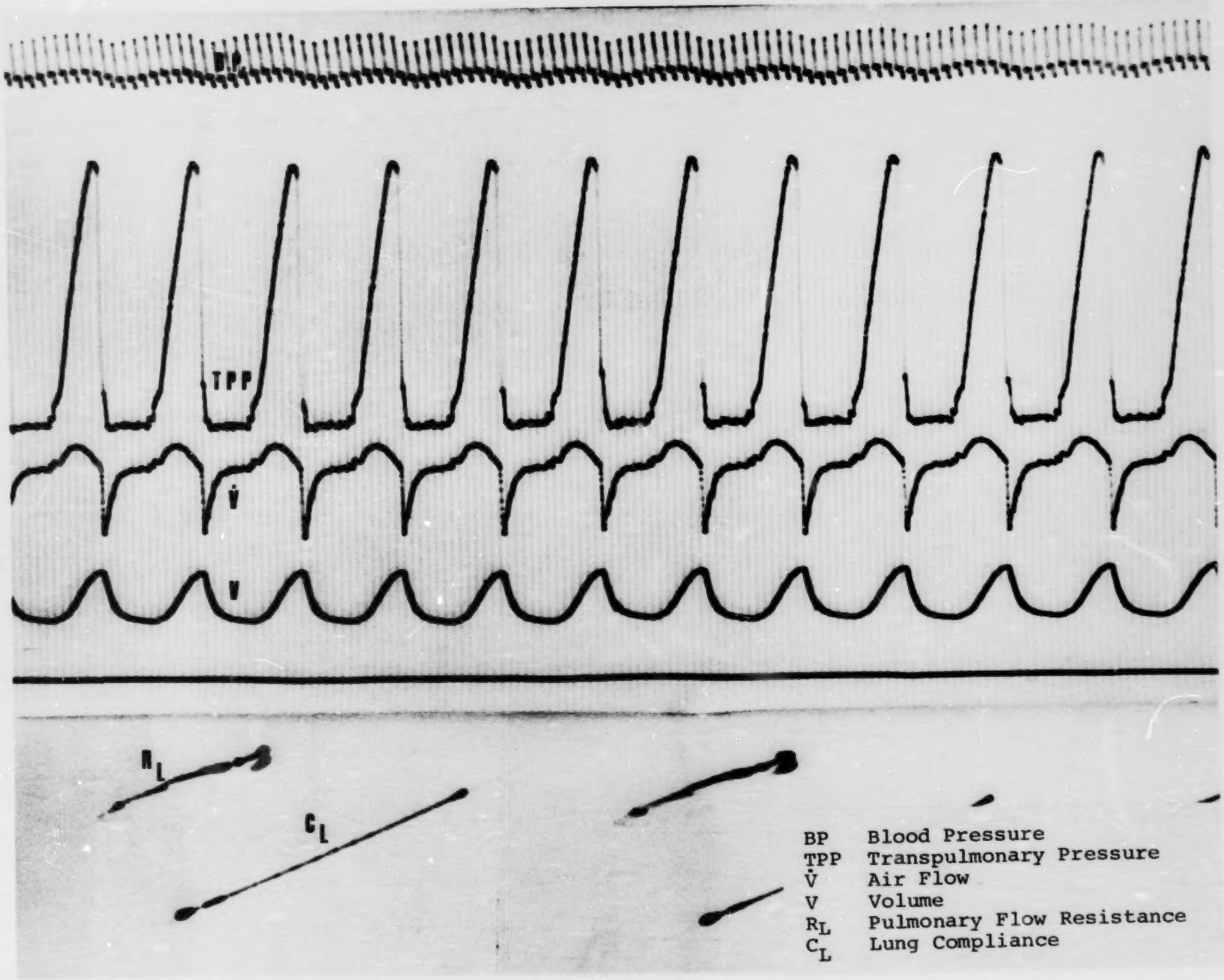
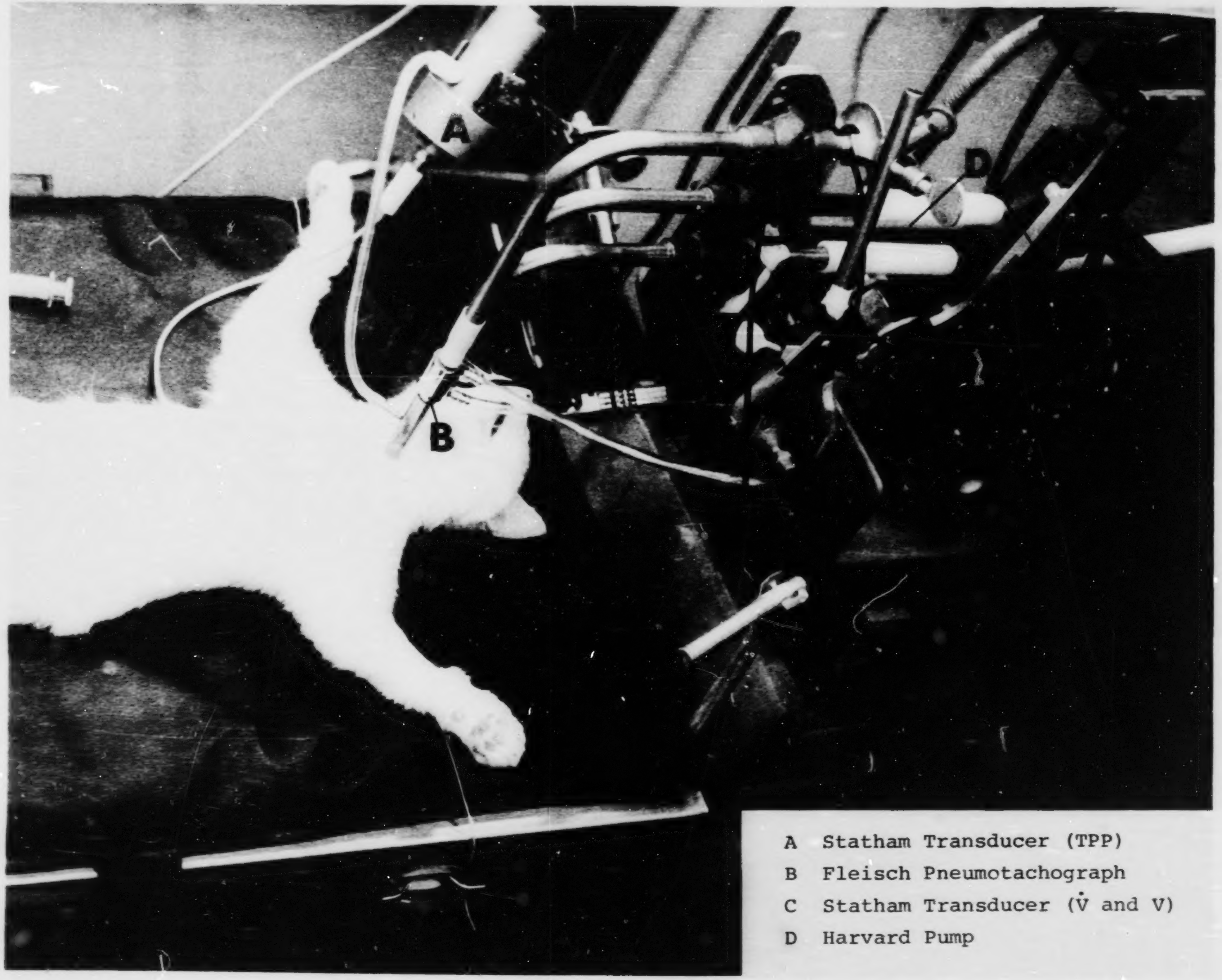

BP
TPP
$\dot{V}$
V
R_L
C_L
BP Blood Pressure
TPP Transpulmonary Pressure
$\dot{V}$ Air Flow
V Volume
R_L Pulmonary Flow Resistance
C_L Lung Compliance

FIGURE 6

PHOTOGRAPH SHOWING CAT ARTIFICIALLY VENTILATED BY HARVARD PUMP



A Statham Transducer (TPP)

B Fleisch Pneumotachograph

C Statham Transducer ($\dot{V}$ and V)

D Harvard Pump

The dead space of the tracheal cannula and Fleisch Pneumotachograph, i.e. volume from bifurcation above Pneumotachograph leading to Harvard pump inlet or discharge, to the trachea of the test animal, was 4.7 cc. A correction was subtracted from each value of total lung resistance in order to correct for the resistance of the tracheal cannula.

E. Conduct of Experiments

Each animal acted as his own control with respect to resting state values of TPP, $\dot{V}$, V, R_L, and C_L. The criterion for significant changes in these parameters following inhalation of polluted air was that the values of these parameters after exposure should be different from the values of these parameters in the same animal before exposure. This approach requires that care be taken to ensure that the animal is in a stable resting state prior to being challenged by a polluted atmosphere. Another criterion of these studies was that following exposure an animal had to return to his initial, preexposure values of these parameters before he was challenged with another polluted atmosphere. These are stringent experimental criteria which resulted in long experiments.

Immediately following surgical preparations the animal was maintained in a resting state for approximately one half hour. This was followed by a 15 minute control period, with recorded records at five minute intervals and continuous sweep visual display. The animal was then tested by mechanical stimulus to ensure the intactness of the vagally mediated reflexes for control of airway constriction(14). Initially, the vagii were surgically isolated and an electrical stimulus was applied, but the mechanical stimulus was judged to be equally effective and less traumatic. A further control period of 15 to 60 minutes followed the mechanical stimulus test. If the vagii were not responsive, as judged by an immediate increase in R_L, then anesthesia was too deep and the animal remained in a resting state until a positive test was obtained for intactness of vagal pathways. This procedure of testing was repeated prior to the first, and after each succeeding pollutant challenge.

The order of exposures in these studies was varied in order to rule out the possibility of a long-term effect due to initial exposure to High SO_2, for instance. Thus, certain animals were initially exposed to High SO_2 (following control period), and then to Low SO_2 or the SO_2-aerosol mixture. All orders of exposure were used. After initial exposure to High SO_2, a 1-2 hour resting period was required to permit the animal to meet the criterion established for return to initial resting values of parameters.

Another series of experiments was performed to determine if receptors which could affect airway size were being bypassed by introduction of pollutant gases (in breathing air) by means of the tracheal cannula. These tests were made with an endotracheal catheter. In this case, the animal was ventilated by the Harvard Pump and the tracheal cannula, but room air (for control) or pollutant laden air was simultaneously flushed through the endotracheal catheter by means of a small pump delivering 2.4 cc/stroke.

Only Low SO_2 concentrations were delivered in these studies.

In a similar manner, a series of tests was performed to determine if receptors in the nose could cause airway constriction. The usual procedures were followed, but another cannula was inserted back to back to the cannula flushing upwards into the mouth. A mask was placed over the nose and mouth. A small pump ventilated the mask while the second cannula served as the exhaust. Thus, the airway above the tracheal cannula was being flushed via the nose and mouth. The lower airways received breathing air or pollutant gas via the original tracheal cannula. Low and High SO_2 in air were used in this series of experiments (Figure 7).

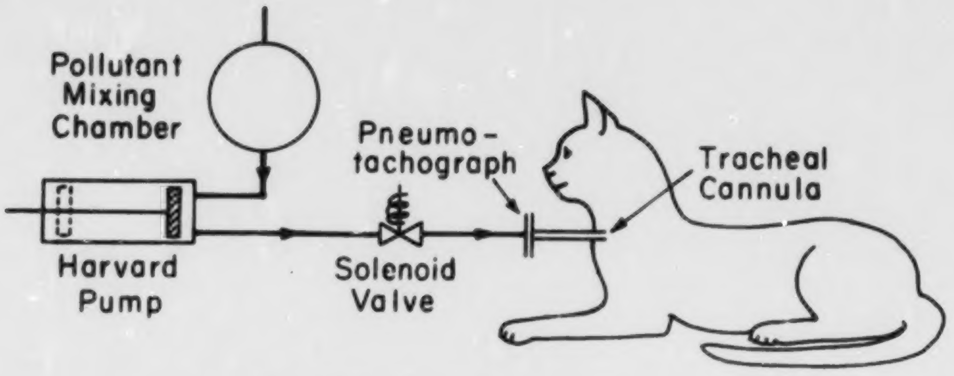
F. Treatment of Data

Values of R_L and C_L were calculated from sweep tracings of $\dot{V}$, V and TPP as described in the original method$^{(1)}$, or the values were obtained from reading recorded loops. R_L and C_L values were then graphed as a function of time. Although continuous records were made, it was necessary to establish the intervals for transcribing data in order to show experimental trends. Figure 8 is a representative graphical summary showing values of R_L and C_L at five minute intervals. In this case each point represents a series of breathing cycles from the sweep record and clearly shows the stability of these parameters during control periods.

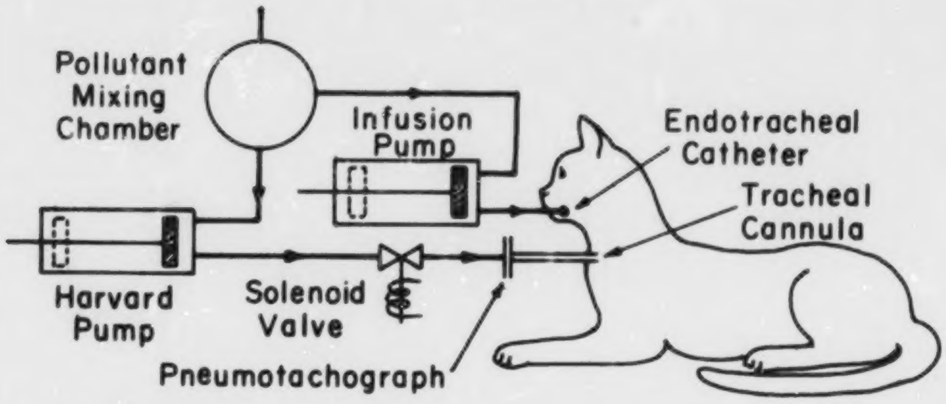
Table 2 contains the numerical results obtained from the experiment on Cat #1610.

FIGURE 7

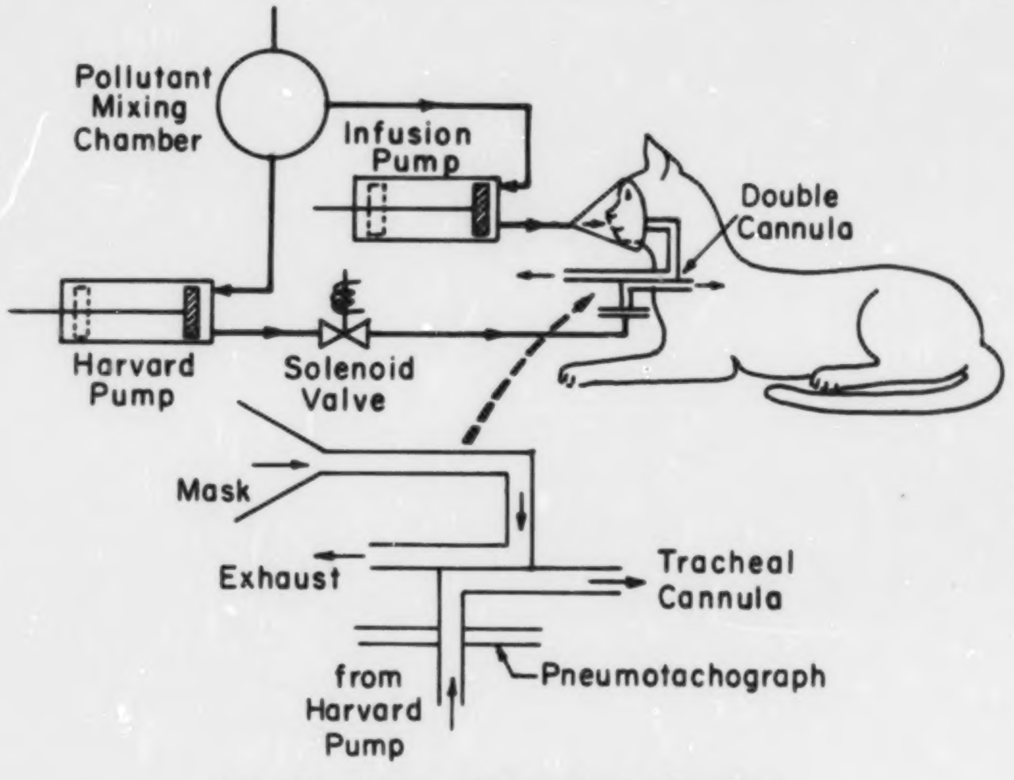
CANNULA ARRANGEMENTS FOR EXPOSURE VIA TRACHEAL CANNULA AND FOR ABOVE AND BELOW TRACHEAL CANNULA


Pollutant
Mixing
Chamber
Pneumo-
tachograph
Tracheal
Cannula
Harvard
Pump
Solenoid
Valve

(a) Via Tracheal Cannula


Pollutant
Mixing
Chamber
Infusion
Pump
Endotracheal
Catheter
Tracheal
Cannula
Harvard
Pump
Solenoid
Valve
Pneumotachograph

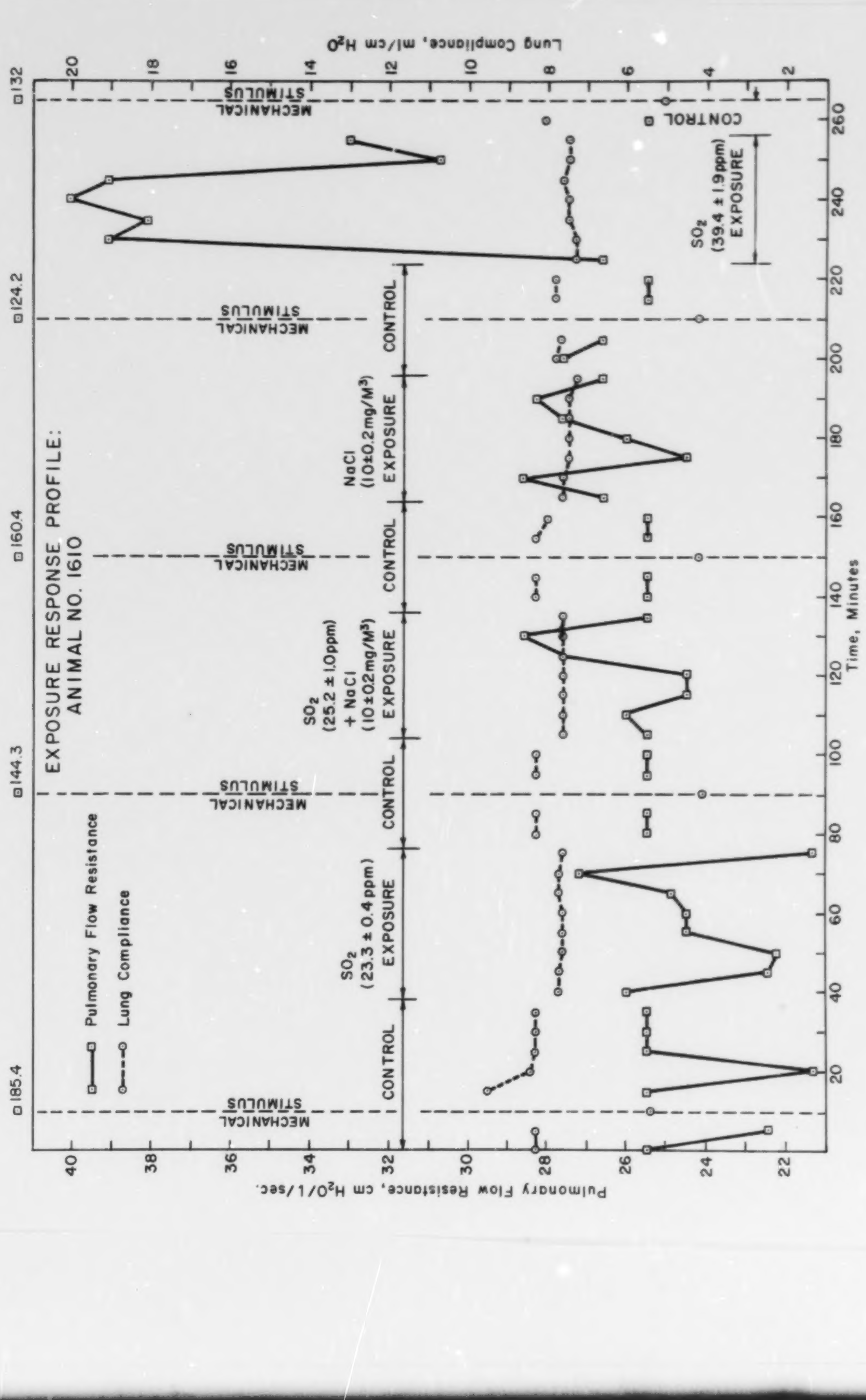
(b) Via Tracheal Cannula and Endotracheal Catheter


Pollutant
Mixing
Chamber
Infusion
Pump
Double
Cannula
Harvard
Pump
Solenoid
Valve
Mask
Exhaust
Tracheal
Cannula
Pneumotachograph
from
Harvard
Pump

(c) Via Naso-pharyngeal Chamber

FIGURE 8

GRAPHICAL SUMMARY OF VARIATIONS IN R_L AND C_L DURING AN EXPERIMENT


EXPOSURE RESPONSE PROFILE:
ANIMAL NO. 1610
Pulmonary Flow Resistance
Lung Compliance
MECHANICAL STIMULUS
CONTROL
SO$_2$ (23.3 ± 0.4 ppm) EXPOSURE
SO$_2$ (25.2 ± 1.0 ppm) + NaCl (10 ± 0.2 mg/M^3) EXPOSURE
NaCl (10 ± 0.2 mg/M^3) EXPOSURE
SO$_2$ (39.4 ± 1.9 ppm) EXPOSURE
185.4
144.3
160.4
124.2
132
Pulmonary Flow Resistance, cm H$_2$O/L/sec.
40
38
36
34
32
30
28
26
24
22
Lung Compliance, ml/cm H$_2$O
20
18
16
14
12
10
8
6
4
2
20
40
60
80
100
120
140
160
180
200
220
240
260
Time, Minutes

Final calculations are based on data from the final fifteen minutes of the control and exposure periods. Other time periods were evaluated, but the last fifteen minute period proved to be the best indication of response. The table shows the mean and the standard arithmetic deviations of parameters during this time period. The percentage change in parameters noted in Table 2 was calculated from control period values as a baseline. Thus,

$$\% \text{ Change} = \left(\frac{\text{Value Following Challenge-Control Value}}{\text{Control Value}}\right) 100$$

Tabular and graphical summaries of individual experiments conducted during this study are contained in the Results and Discussion section of this report.

Before an animal's response was termed "significant" it was necessary to compare R_L and C_L values obtained during the last fifteen minutes of the control and exposure periods. The comparison was based on a modified Student t-test for the difference of means. The degrees of freedom (d.f.) for the test was calculated from the variances and sample sizes. Thus,

$$t = \frac{\bar{x}_2 - \bar{x}_1}{\sqrt{S_1{}^2/n_1 + S_2{}^2/n_2}}$$

$$\text{d.f.} = \frac{[(S_1{}^2/n_1) + (S_2{}^2/n_2)]^2}{(S_1{}^2/n_1)^2/(n_1 + 1) + (S_2{}^2/n_2)^2/(n_2 + 1)} - 2$$

where mean values are designated $\bar{x}_1$ and $\bar{x}_2$, the standard deviations are S_1 and S_2, and sample sizes are n_1 and n_2.

The level of significance accepted as meaningful with the t-test was $P < 0.01$ (two tailed test).

TABLE 2

Cat No. 1610

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

	Pulmonary Flow Resistance (b)														
	Control	Mech. Stim.	% Change	Control	Low SO_2	% Change	Control	Mech. Stim.	% Change	Control	SO_2+ NaCl	% Change	Control	Mech. Stim.	% Change
	25.5	185.4	674.1	25.5	24.9	-2.4	25.5	144.3	465.9	25.5	27.6	8.2	25.5	160.4	529.0
	22.4			25.5	27.2	6.7	25.5			25.5	28.6	12.2	25.5		
				25.5	21.3	-16.5					25.5	0			
Mean±	24.0	185.4		25.5	24.5		25.5	144.3		25.5	27.2		25.5	160.4	
S.D.	2.2			0	3.0		0			0	1.6		0		
	REFLEX INTACT			ΔN.S.			REFLEX INTACT			ΔN.S.			REFLEX INTACT		
	Lung Compliance (c)														
	Control	Mech. Stim.	% Change	Control	Low SO_2	% Change	Control	Mech. Stim.	% Change	Control	SO_2+ NaCl	% Change	Control	Mech. Stim.	% Change
	8.3	5.4	-34.9	8.3	7.7	-7.2	8.3	4.1	-50.6	8.3	7.6	-8.4	8.3	4.2	-49.4
	8.3			8.3	7.7	-7.2	8.3			8.3	7.6	-8.4	8.3		
				8.3	7.6	-8.4					7.6	-8.4			
Mean±	8.3	5.4		8.3	7.6		8.3	4.1		8.3	7.6		8.3	4.2	
S.D.	0			0	0.1					0	0		0		
				P<0.01						P< 0.01					
Sequence of Challenge (a)	(1)			(2)			(3)			(4)			(5)		

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm H_2O/1/sec.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant (P>0.05)

TABLE 2 (Continued)

Cat No. 1610

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

	Control	NaCl	% Change	Control	Mech. Stim.	% Change	Control	High SO_2	% Change	Control	Mech. Stim.	% Change	
Pulmonary Flow Resistance (b)													
	25.5	27.6	8.2	27.6	124.7	358.3	25.5	39.1	53.3	25.5	132	417.6	
	25.5	28.3	11.0	26.6			25.5	30.7	20.4				
		26.6	4.3					33	29.4				
Mean ±	25.5	27.5		27.1	124.7		25.5	34.3		25.5	132		
S.D.	0	0.8		0.7			0	4.3					
	Δ N.S.			REFLEX INTACT			Δ N.S.			REFLEX INTACT			
Lung Compliance (c)													
	8.3	7.5	-8.0	7.8	4.2	-45.8	7.8	7.6	-2.6	8.1	5.1	-37.0	
	8.0	7.5	-8.0	7.7			7.8	7.5	-3.8				
		7.3	-10.4					7.5	-3.8				
Mean ±	8.2	7.4		7.7	4.2		7.8	7.5		8.1	5.1		
S.D.	0.2	0.1		0.1			0	0.1					
	$P < 0.05$						$P < 0.05$						
Sequence of Challenge (a)	(6)			(7)			(8)			(9)			

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm H_2O/l/sec.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

G. Pathological Procedures

Six weeks after fixation tissues were removed from freezer and Carnoy's fluid poured off. The Storey and Staub(15) method was used to process and stain most of the lung tissues except for a modification as follows:

1. Nitrocellulose embedded tissues were sectioned 75 μm thick on a Reitchert sliding microtome. Using Lundy's method, serial sections were stapled in sequence, approximately 5 mm apart (by means of an office stapling machine), on a strip of 500 gauge polyethylene film, cut slightly wider than the width of the sections. The length of the strips was determined by the size of our staining dishes (Pyrex Baking Dish 5" x 9"). After the tissue was stained, sections were detached from the film with scissors and mounted in sequence on numbered slides. Strips of polyethylene film holding sections not immediately required for staining were rolled up and stored in 70% alcohol.

In order to obtain thin sections, a small piece of each lung tissue was put into Bouin's fluid for 24 hours for further fixation. A routine manual process was used to obtain paraffin blocks. Blocks were sectioned 5 μm on an American Optical rotary microtome. Serial sections were stained with Harris Hematoxylin and Eosin and mounted on glass slides with permount.

We photographed serial sections 5 μm thick and 75 μm thick with a Zeiss photomicroscope. To obtain a total estimated magnification of 130x, a planachromate 2.5x objective with an N.A. = 0.08, optavar = 2.0x, intermediate camera magnification of 3.2x and photographic enlargement estimated at 8.0x was used. A calibrated field finder was used in returning to the same photographic field of each slide in the series.

Measurements were made of the alveoli on the enlarged prints of thick tissue sections. We noted in our findings that there were no significant changes in the sizes of the small conducting airways of cats which had shown small R_L and small C_L changes.

In an attempt to measure the same segment of lung lobe of each cat we measured 2 cm from the tip of the third lobe of the right lung and removed that portion of the lobe for frozen sectioning and for comparison. Biological factors such as weight and size of the lungs presented a problem. We questioned whether we could be sure that we were in the same segment of the lobe, when some of the lungs were larger than others. Despite this obvious flaw, we cut the same distance from the tip of the same lobe of each animal to obtain comparable sections. We realized, however, that we had encountered a source of error in using a method of measurement on a histologic section.

Thin lung sections were studied, of cats that had been challenged with SO_2 in the air and SO_2 + NaCl aerosol in medical grade breathing air. The absence of comparable changes in cell structures suggested that small R_L changes and small C_L changes could not be detected histologically.

III. RESULTS AND DISCUSSION

All calculated results for individual experiments are contained in tabular and graphical summaries in this Section. The results presented were obtained by extracting data from continuous records as described in Section II F., above. Results are presented for a total of twenty-nine complete experimental protocols in which twenty-nine different cats were used. A discussion of this vast amount of data requires that a simple summary be used to present findings. The reader can examine calculated results of individual animal experiments to substantiate generalizations made in this discussion.

A. Changes in Pulmonary Flow Resistance and Lung Compliance in Cats Following Pollutant Challenges

Table 3 summarizes the challenge atmospheres which produced significant changes in pulmonary flow resistance or lung compliance when the pollutant mixture was administered via tracheal cannula. Table 4 is a similar summary for pollutants administered via endotracheal catheter and via double cannula to produce pollutant flushing of the nasopharyngeal chamber and any receptors above the trachea cannula. First, the data suggest that with the cat, approximately 20 ppm SO_2 in air are required before any animals show significant alterations in R_L. Prior to the studies reported here, it had been shown$^{(7)}$ that pure SO_2 delivered into the lower airways and lungs during a single respiratory cycle increased R_L (mean, + .246 percent; $P < 0.05$). The animal returned to control levels within one minute$^{(7)}$. The work reported here indicates that with the same physiological preparation approximately 20 ppm SO_2 in air are required to trigger this response--and at this concentration only two animals in twenty responded. One animal in twenty showed a significant decrease in R_L at this concentration.

It is interesting to compare concentrations of SO_2 in air required to cause bronchoconstriction in different species. Frank, et al.(16) demonstrated a significant increase in resistance to air flow in volunteers exposed to 5 ppm. This finding is consistent with that of Burton, et al. (Appendix I) of perhaps one out of ten "human reactors" to approximately 3 ppm SO_2 in air. Balchum, Dybicki and Meneely(17) exposed ten anesthetized dogs to concentrations of SO_2 in air ranging from 1.8 to 148 ppm for periods from 30 to 40 minutes. Increases in the non-elastic resistance to breathing ranged from 150 to over 300% and these increases occurred within nine seconds after the onset of breathing SO_2; increases disappeared as quickly following the end of exposure. Exposures of guinea pigs to SO_2 in air for one hour results in a 10% increase in preliminary flow resistance at 0.16 ppm(18). The guinea pig, as used by Amdur, "may be the accidental analog of the sensitive segment of the population"(3). The results reported here suggest that the cat, as used in our preparation, is an analog of the more resistant segment of the population.

An aspect of our studies which was stressed by Frank, et al.(15) and Burton, et al. (Appendix I) in studies involving human exposures but was not stressed in studies employing dogs or guinea pigs, is the great variability of response of individuals. In our studies, "reactors" were characterized by large variability of response in R_L and C_L and hypersensitivity during preparation. Examination of graphical summaries of results of exposures will demonstrate the great variability of response for animals with cervical vagosympathetic nerve conduction intact.

Two other characteristics of response should be noted for their contrast with guinea pig studies. Our animals returned to control levels shortly after exposure, although we often waited for an extended period to reduce the range of variation about the mean R_L or C_L following exposure, i.e. variability about the mean was greater following exposure, which we did not desire. We chose to permit the animal to settle down. The guinea pig, on the other hand, returns slowly to control levels after exposure. As noted above, following exposure human subjects and dogs also return rapidly to control values of resistance to air flow.

In animals showing changes in pulmonary flow resistance, we confirmed the effects of cooling the vagii, injection of atropine or severing the vagii, on blocking these changes, as reported by Nadel, et al.(7)

Table 4 summarizes results collected to focus on the sites of receptors responsible for bronchoconstriction or peripheral airway constriction. These results relate to findings of nearly total uptake of SO_2 in air in the nose and upper airways in animals(19,20) and in human subjects(21). Less than 1% of the inhaled concentration of SO_2 in air is estimated to reach the larynx and more distal airways in man(20). The endotracheal catheter and double cannula were used in these studies to determine if the number of animals responding increased, or the degree of response increased in respondents when the pollutant mixtures were administered via these pathways in cats. Three animals were exposed with the endotracheal catheter and two with the double cannula. Unfortunately, these experiments must be contrasted to findings in twenty cats where a tracheal cannula was used for delivery of pollutant mixtures. However, comparison of Tables 3 and 4 suggest that delivery of pollutant via tracheal cannula did evoke fewer significant responses in R_L or C_L, thus suggesting that certain receptors were bypassed when pollutant was delivered by tracheal cannula. Thus, our findings suggest that receptors in the nasal pharyngeal chamber and proximal to the tracheal cannula used here can increase total lung resistance distal to the tracheal cannula. This finding contrasts with that by Nadel and Widdicombe(22) that mechanical irritation of the nasal mucosa did not change total lung resistance in cats anesthetized with chloralose and urethan. Additional cats should be studied to substantiate our findings.

Small but insignificant changes in lung compliance were found in a few animals following each of the challenges presented, including one animal who showed a significant decrease in C_L following inhalation of NaCl aerosol. These results suggest that the physiological mechanisms generally delineated for upper airway and for peripheral airway constriction by acute challenges of physical or chemical agents may not be completely independent. Other investigators have suggested that a reflex mediated by vagal efferent fibers could partially contribute to peripheral airway changes(8). Alternately, the small quantities of pollutants which penetrated the upper airways may be sufficient to cause peripheral airway constriction, but this possibility, although suggested elsewhere(21), seems remote to us as a mechanism for peripheral airway constriction.

Finally, it should be noted that while upper airway changes after inhalation of pollutants could be due to mucous secretion, cooling of vagii, intravenous atropine or deep anesthesia blocked these changes, thus suggesting that they were due to changes in airway calibre.

B. Changes in Pulmonary Flow Resistance and Lung Compliance in Guinea Pigs Following Pollutant Challenges

The rapid return of C_L and R_L values in cats, dogs and man following exposures to pollutants used in this study differs from the slow recovery of guinea pig pulmonary flow resistance following similar exposures. Therefore, we used the exact experimental preparations described above to study the responses of guinea pigs. Animals weighing approximately one kilogram were used to permit insertion of a tracheal cannula; a difficult procedure with small animals.

It was not possible to obtain valid data for guinea pigs with our preparation. The animals secreted abundant mucous

TABLE 3

SUMMARY OF R_L[a] AND C_L[b] RESPONSES (P > 0.01) OF CATS EXPOSED TO POLLUTANT MIXTURES IN THIS STUDY
(TRACHEAL CANNULA POLLUTANT DELIVERY)

Challenge	Low Concentration of SO_2 in Air[c]				SO_2[d] and NaCl Aerosol[e] in Air				NaCl Aerosol in Air[e]				High Concentration SO_2 in Air[f]			
Cat	R_L		C_L		R_L		C_L		R_L		C_L		R_L		C_L	
Number	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-
1482g														x		
1117																
1112	x												x			
1113																
1564														x		
1566				x												
1144	x															
1593																x
1606																
1611																
1610				x				x								
1633																
1612				x							x					
1609																
1651			x													
35354g,i																
32135g,i																
1486g,i		x		x				x								
1487g,i				x				x								
1676g,i				x					x				x			
1781h																x
1801h												x				
1988h				x				x						x		
1807h				x								x			x	

[a] R_L = Pulmonary Flow Resistance, Cm H_2O/l/sec (+ denotes increase, - denotes decrease).

[b] C_L = Lung Compliance, ml/Cm H_2O (+ denotes increase, - denotes decrease).

[c] SO_2 in air concentration for all exposures, expressed as Mean ± S.D. = 19.0 ± 5.9 ppm.

[d] SO_2 in air concentration for all exposures, expressed as Mean ± S.D. = 17.9 ± 8.3 ppm.

[e] NaCl aerosol in air concentration, expressed as Mean ± S.D. = 10 ± 0.2 mg/m^3.

[f] SO_2 in air concentration for all exposures, expressed as Mean ± S.D. = 34.6 ± 12.3 ppm.

[g] In the following experiments, the Low Concentration of SO_2 in air was the first challenge followed by Control Period SO_2+NaCl Aerosol, etc.

[h] In the following experiments, the High Concentration of SO_2 in air was the first challenge, followed by Control Period NaCl Aerosol, etc.

[i] These animals were characterized by extreme values of SO_2 concentration.

TABLE 4

SUMMARY OF R_L[a] AND C_L[b] RESPONSES (P 0.01) OF CATS EXPOSED TO POLLUTANT MIXTURES IN THIS STUDY (ENDOTRACHEAL CATHETER POLLUTANT DELIVERY)

Challenge	SO_2 in Air Via Tracheal Cannula[c]				SO_2 in Air Via Endotracheal Catheter[d]				SO_2 in Air Via Both Sites[e]			
Cat Number	R_L		C_L		R_L		C_L		R_L		C_L	
	+	-	+	-	+	-	+	-	+	-	+	-
2984		x								x		
2206				x								x
53869				x				x				x

SUMMARY OF R_L[a] AND C_L[b] (NASO-PHARYNGEAL FLUSH WITH DOUBLE CANNULA)

Challenge	Low Concentration of SO_2 in Air[f]				High Concentration SO_2 in Air[g]			
Cat Number	R_L		C_L		R_L		C_L	
	+	-	+	-	+	-	+	-
2393								
5674								

[a] R_L = Pulmonary Flow Resistance, Cm H_2O/1/sec (+ denotes increase, - denotes decrease).

[b] C_L = Lung Compliance, ml/Cm H_2O (+ denotes increase, - denotes decrease).

[c] SO_2 in air concentration for all exposures, expressed as Mean ± S.D. = 18.2 ± 1.9 ppm.

[d] SO_2 in air concentration for all exposures, expressed as Mean ± S.D. = 17.2 ± 0.9 ppm.

[e] SO_2 in air concentration for all exposures, expressed as Mean ± S.D. = 17.1 ± 0.9 ppm

[f] SO_2 in air concentration for all exposures, expressed as Mean ± S.D. = 14.4 ± 1.8 ppm.

[g] SO_2 in air concentration for all exposures, expressed as Mean ± S.D. = 22.5 ± 2.9 ppm.

which required frequent withdrawal by catheter connected to a suction source. The changes in pulmonary mechanics which stemmed from mucous secretion in control animals would have overwhelmed any changes associated with airway calibre alterations due to pollutants. Mucous secretion under these conditions cannot be compared to that which may occur during spontaneous breathing during exposure to pollutants, the conditions for Amdur's studies(3). However, the slow return to control values of R_L by guinea pigs strongly suggests mucous secretion as a contributor to R_L, a hypothesis which could be easily tested experimentally.

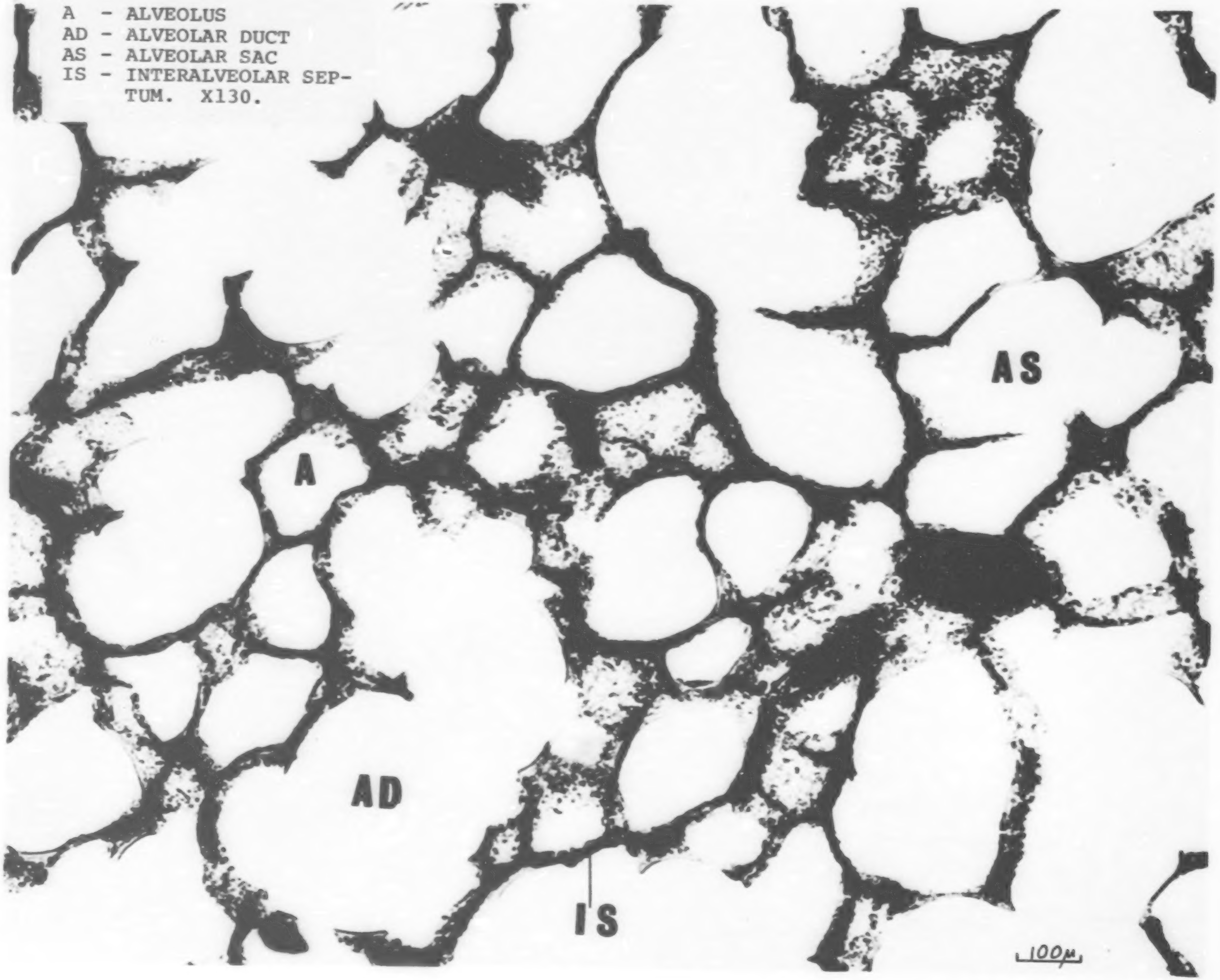
C. Pathological Changes in Cats Following Pollutant Exposures

Rapid lung freezing procedures and preparation of samples were described above. While alterations in airway calibre could be detected by this method following severe acute pollutant challenges(8), it was not possible to detect differences in airway calibre in thick and thin lung sections of control and exposed animals in the studies reported here. A control animal was one previously exposed to SO_2 or SO_2-aerosol mixture in air, but whose pulmonary flow resistance subsequently returned to the preexposure value. Figures 9 and 10 show the close correspondence between photomicrographs of thick lung sections from a control and an exposed animal, respectively. Figure 11 is a photomicrograph of a typical thin lung section.

The work of Macklem and Mead(23) stimulated these attempts to detect changes in peripheral airway size when alterations in pulmonary flow resistance were present. Macklem and Mead demonstrated that at high lung volumes, R_L increased and this resistance was almost entirely due to that between airways 1.5-2.5 mm and the trachea in dogs. Thus, large changes in peripheral airways resistance could go undetected by measurement of R_L, which is insensitive to alterations in peripheral airway resistance. Our studies show that careful morphological examination of airway calibre are also insensitive to any changes that may occur in the ranges of R_L increases cited here.

FIGURE 9

PHOTOMICROGRAPH OF A THICK SECTION OF THE RIGHT LUNG LOBE OF A MALE CAT (NO. 1112). FROZEN IMMEDIATELY AFTER CAT HAD RETURNED TO CONTROL STATE FOLLOWING 15 MINUTES PREVIOUS EXPOSURE TO 27 PPM SO_2.

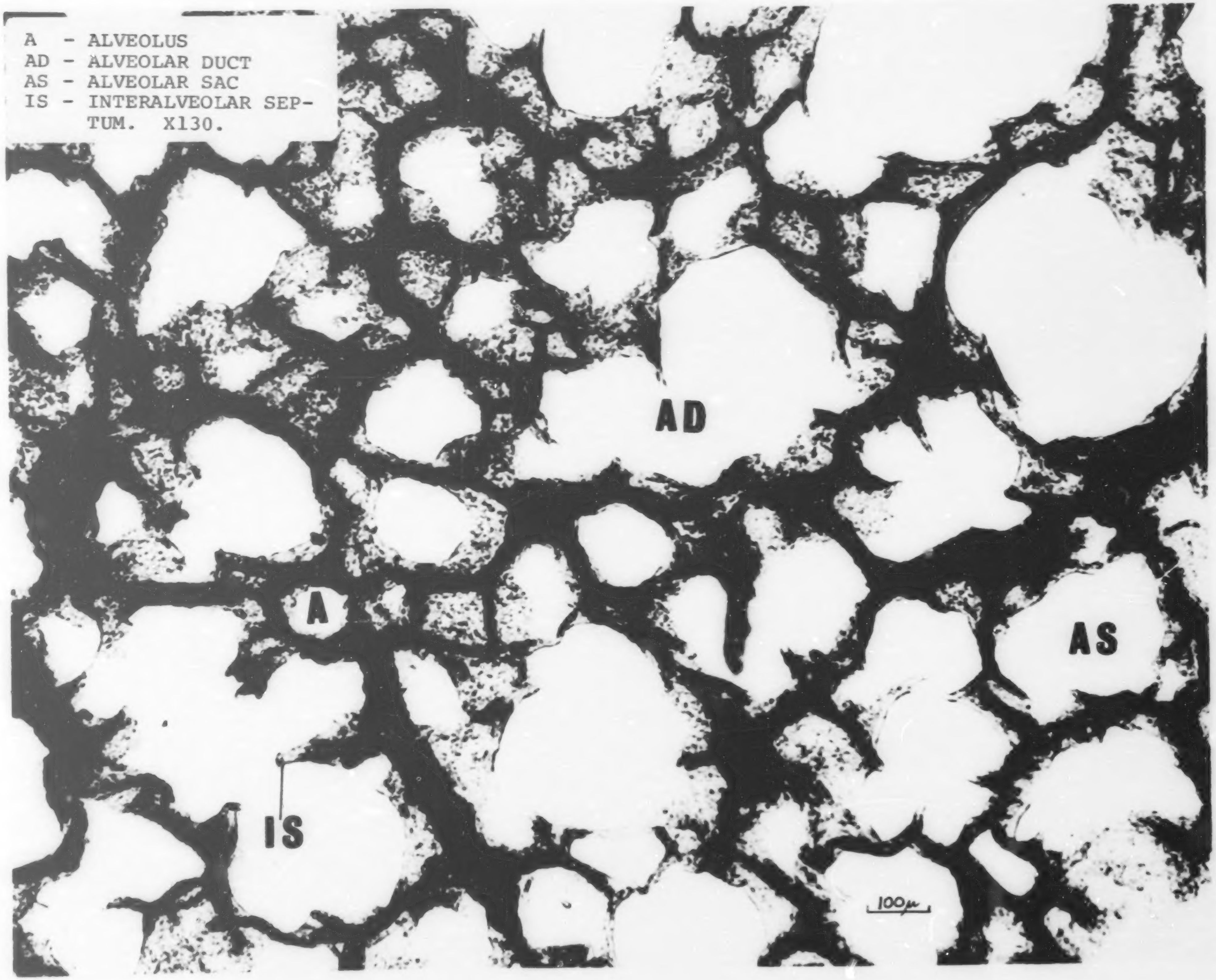


A - ALVEOLUS
AD - ALVEOLAR DUCT
AS - ALVEOLAR SAC
IS - INTERALVEOLAR SEPTUM. X130.

AS
A
AD
IS
100µ

FIGURE 10

PHOTOMICROGRAPH OF A THICK SECTION OF THE RIGHT LUNG LOBE OF A FEMALE CAT (NO. 1144). FROZEN IMMEDIATELY FOLLOWING EXPOSURE TO 40 PPM SO_2 FOR 30 MINUTES.

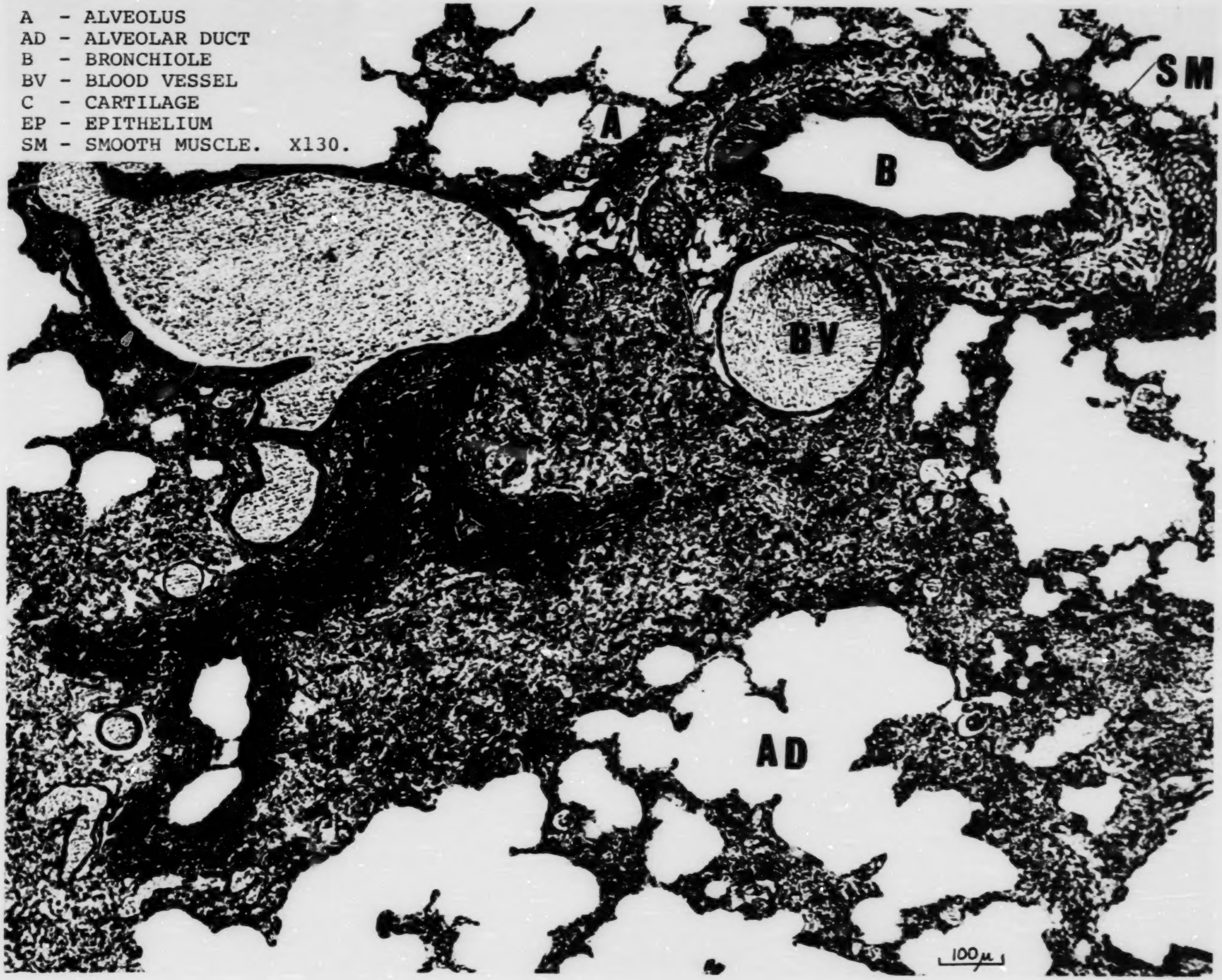


A - ALVEOLUS
AD - ALVEOLAR DUCT
AS - ALVEOLAR SAC
IS - INTERALVEOLAR SEPTUM. X130.

AD
AS
A
IS
100μ

FIGURE 11

PHOTOMICROGRAPH OF A THIN SECTION OF THE RIGHT LUNG LOBE OF A MALE CAT (NO. 1610). FROZEN AFTER CAT HAD RETURNED TO CONTROL STATE FOR 15 MINUTES FOLLOWING PREVIOUS EXPOSURES TO 40 PPM SO_2.



A - ALVEOLUS
AD - ALVEOLAR DUCT
B - BRONCHIOLE
BV - BLOOD VESSEL
C - CARTILAGE
EP - EPITHELIUM
SM - SMOOTH MUSCLE. X130.

A
SM
B
BV
AD
100µ

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APPENDICES

A. Reprint of "Response of Healthy Men to Inhaled Low Concentrations of Gas-Aerosol Mixtures" by Burton, G. G., Corn, M., Gee, J. B. L., Vasallo, C., and Thomas, A. P. AMA Arch. Env. Hlth. 18, 681 (1969).

B. Tabular and Graphical Records of Individual Experiments.

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Response of Healthy Men to Inhaled Low Concentrations of Gas-Aerosol Mixtures

George G. Burton, MD; Morton Corn, PhD; J. Bernard L. Gee, MD; Charles Vasallo, MD; and Armand P. Thomas, BA, Pittsburgh

EXISTING laboratory studies dealing with the acute effects of inhaled pollutants in humans and experimental animals have recently been reviewed.[1] These studies had failed to demonstrate changes in lung mechanics of healthy adults exposed to single pollutants at concentrations representative of those in ambient urban air. LaBelle et al[2] and later Goetz[3] had suggested that gas-aerosol synergism might explain the hypothesized adverse effect on health, and the animal studies of Amdur et al[4,5] gave the weight of considerable sound experimental data to the concept.

Several studies have been done, to date, to determine the presence or absence of gas-aerosol synergism in man, and the results are conflicting. Frank et al[6] using mixtures which consisted of SO_2 and a submicron NaCl aerosol, could demonstrate no synergistic effect in healthy adults over the range of 1 to 17 ppm SO_2. Also, no significant changes in pulmonary flow resistance (R_L) occurred during exposure to 1 to 2 ppm SO_2 with or without the added aerosol.

Later, Toyama[7] studied the effects of a wide range of concentrations of SO_2 alone and in combination with a monodisperse submicronic aerosol of NaCl (concentration, 7.4 mg/cu m). He concluded that a synergistic response producing increased airway resistance was present, even at low concentrations of SO_2, though the number of

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Table 1.—*Exposure Concentrations of SO$_2$ and NaC1 Aerosol**

Pollutants	Experimental Subjects 6	7	8	10	9	1	2	3	5	4	Mean—All Subjects
SO$_2$ (10 ft)	1.9 ±0.00	3.0 ±0.08	2.4 ±0.15	3.2 ±0.13	2.1 ±0.00	2.2 ±0.00	1.4 ±0.14	1.2 ±0.05	1.9 ±0.56	1.9 ±0.00	2.1 ±0.19
SO$_2$ (20 ft)	1.9 ±0.13	3.1 ±0.11	2.8 ±0.28	3.6 ±0.00	1.9 ±0.06	2.1 ±0.03	1.2 ±0.03	1.2 ±0.08	1.8 ±0.22	1.7 ±0.04	2.1 ±0.2[illegible]
Aerosol Mix (10 ft)	1.9 ±0.09	3.0 ±0.00	2.3 ±0.10	3.0 ±0.03	1.9 ±0.18	2.3 ±0.10	1.4 ±0.02	1.2 ±0.02	1.4 ±0.07	1.1 ±0.14	2.0 ±0.22
Aerosol Mix (20 ft)	1.9 ±0.03	3.0 ±0.00	2.4 ±0.22	3.3 ±0.16	1.7 ±0.11	1.9 ±0.03	1.2 ±0.12	1.1 ±0.08	1.8 ±0.25	1.8 ±0.08	2.0 ±0.22
[NaCl]	2.4 mg/cu m	2.0 mg/cu m	2.0 mg/cu m	2.7 mg/cu m	2.1 mg/cu m	2.5 mg/cu m	2.3 mg/cu m	2.1 mg/cu m	2.0 mg/cu m	2.2 mg/cu m	2.2 ±0.08

* SO$_2$, parts per million; NaCl, mg/cu m. Values are mean ± 1 SE.

subjects exposed to < 5.0 ppm SO$_2$ and aerosol was small.

At the sixth annual Air Pollution Medical Research Conference in 1963, Toyama[8] presented studies of eight healthy young men whom he exposed to SO$_2$ concentrations (3 to 40 ppm) with and without inhalations of Kawasaki industrial area dusts (concentration, 10 to 50 mg/cu m). Again, he concluded that a synergistic response could be demonstrated, though there were "fairly wide individual differences."

We decided to extend these studies by measuring airway resistance (R$_A$)—a more easily performed test of irritant response—and R$_L$, during precisely controlled and characterized pollutant exposures. Furthermore, our studies were designed to detect possible changes following pollutant exposure at concentrations which resembled those found in urban air.

Materials and Methods

Subject Exposure Procedure and Pulmonary Mechanics Measurement.—Studies were performed using ten healthy men volunteers ranging in age from 25 to 34 years as subjects. All subjects had no previous history of, or physical findings suggesting significant cardiopulmonary disease. Five were cigarette smokers; five were not.

Pulmonary flow resistance (R$_L$) was measured with an esophageal balloon and a low resistance spirometer using the technique of Mead and Whittenberger.[9] Recordings of flow, volume, and esophageal (intrapleural) pressure were made on a multichanel galvanometric recorder. Airway resistance (R$_A$) was measured using the body plethysmograph airway-interruption technique of the same authors.[10] Thoracic gas volume (TGV) was determined by a technique modified after Dubois et al[11]: Apparatus resistance across the R$_L$, C$_L$ apparatus was 0.38 cm H$_2$O at 1 liter/sec; across the tubing of the plethysmograph it was 0.51 cm H$_2$O at 1 liter/sec. Since Widdicombe and Nadel[12] had suggested that work of breathing should increase with increasing respiratory frequency (f) and airflow velocities, particularly if total airways dead space (V$_D$) is increased, we measured compliance (C$_L$) and R$_L$ during normal resting and forced ventilation at airflows which did not exceed 2.5 liters/sec.

The subjects wore nose clips and mouthbreathed, warmed, humidified filtered medical-grade air from the dilution board schematically described below. Air-breathing measurements were made after five minutes, first on the low resistance spirometer and then in the body plethysmograph. Measurements of lung resistance and compliance were complete within one minute following exposure; the plethysmograph data were obtained within the following two minutes. We felt that earlier measurements of these parameters were unnecessary, and did not attempt to make the exposures in the plethysmograph itself. Subject comfort during the hour-long total exposure was a factor in our decision to proceed in this fashion.

After control measurements were made, the subject was then exposed to SO$_2$ or an SO$_2$-sodium chloride aerosol mixture. The order of exposure to gas or gas-aerosol mixture was randomized. The exposures lasted 30 minutes each, with measurements being made at 10 minutes and 30 minutes. Sufficient time was allowed between exposures to allow airway and total lung resistance to return to control levels, if any change had occurred. Of 19 studies performed, ten successfully fulfilled the complete criteria of the experimental protocol.

Pollutant Aerosol and Gas Generation and Characterization.—Pollutant mixtures for the

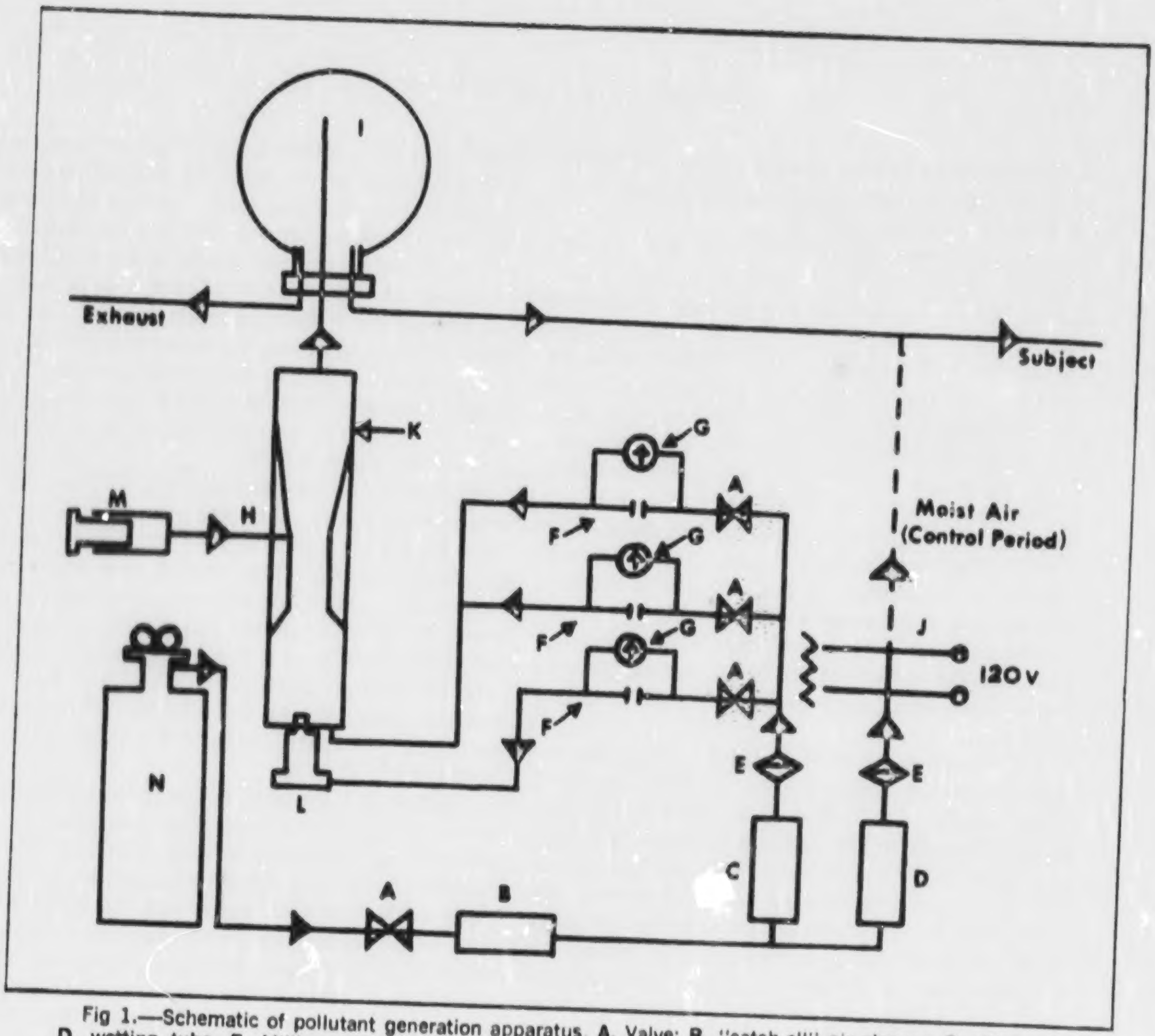
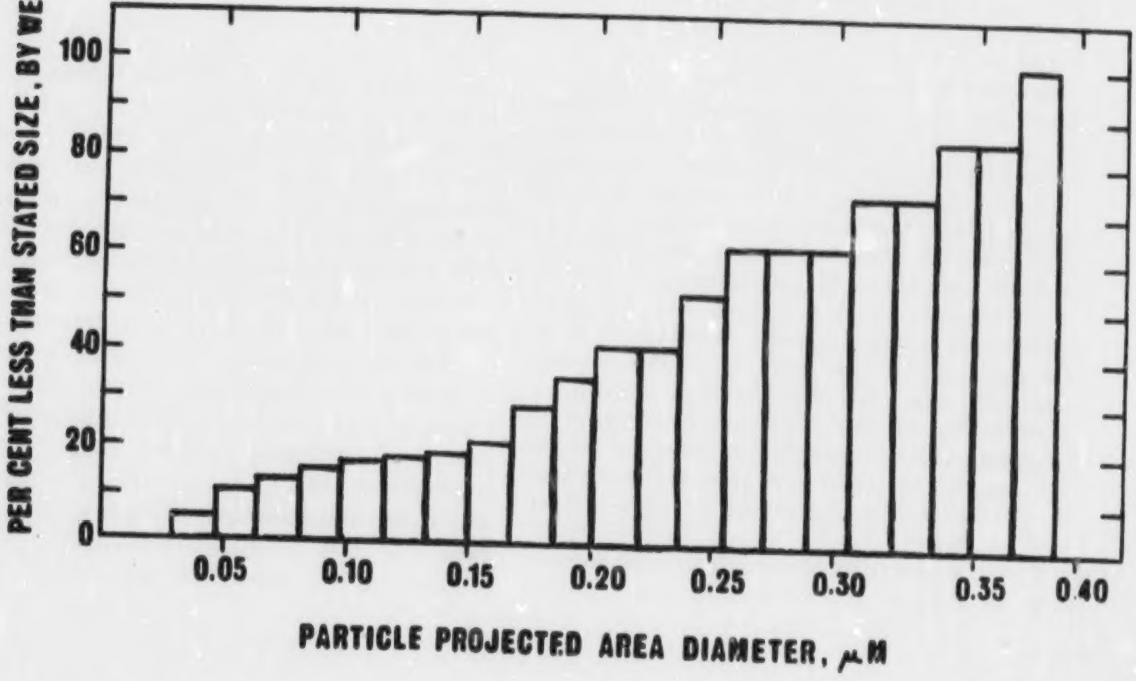

I
Exhaust
Subject
K
G
M
H
Moist Air
(Control Period)
F
A
J
120 v
N
L
E
C
D
B

Fig 1.—Schematic of pollutant generation apparatus. A, Valve; B, "catch-all" air cleaner; C, silica gel; D, wetting tube, E, Millipore HA filters; F, critical orifice; G, pressure gage, H, SO_2 inlet, I, mixing balloon; J, heating coil with rheostat control, K, Herschel-Type Vent, in Tube, L, Dautreband D_{30}1, M, motor driven syringe; N, medical grade compressed air; triangle, flow direction.

Fig 2.—Cumulative particle—size distribution curve for test aerosols (NaC1), sized at 32,000 × with Zeiss TGZ-3 electron microscope.



exposures were produced using a portable aerosol-gas supply apparatus designed and constructed for this study (Fig 1).

Medical-grade compressed air was passed through activated carbon and silica gell, moistened and warmed, then metered by the use of calibrated orifices, before entering the Dautrebande D_{30}1 generator or the Venturi tube for mixing with aerosol and gas. Sulfur dioxide gas was supplied to the Venturi throat by a syringe driven by an infusion pump. The Dautrebande D_{30}1 aerosol generator was filled with 0.225% by weight solution of NaCl and placed in an opening at the base of the Venturi tube. The salt solution was replaced every 15 minutes to prevent a significant increase in NaCl concentration due to the evaporation of water.

The mixture exited from the Venturi mixing tube into a reservoir balloon, where it was either exhausted, or withdrawn by the subject under test.

All components of the system, with the exception of the balloon were of stainless steel, rigid plastic, or Teflon. The aerosol mixture was delivered to the subject through a 1-inch stainless steel Teflon-lined tube. At the end of the tube was a three-way valve. One port was connected to the "control" air source; the other port was attached to a two-way "J" valve. An exhaust line was connected to the outlet side of the "J" valve. A moulded contour rubber mouthpiece which fitted inside the mouth of the subject was used. Care was taken during the exposures to keep saliva from collecting inside of the "J" valve.

Measurement of pollutant concentration during exposures were made through a stainless steel tap which was injected into the inspiratory side of the breathing valve as close to the mouth as possible.

In order to determine SO_2 concentration, 2.8 liters/min of the pollutant mixture was drawn for two minutes into a midget impinger containing 50 ml of West-Gaeke reagent. The samples were then analyzed spectrophotometrically using the modified West-Gaeke method.[13]

During the first ten-minute exposure, two samples were taken, four minutes apart. During the 20-minute exposure three samples were taken at six-minute intervals. Whenever sodium chloride aerosol was present in the system, sampling was performed by first drawing a sample through HA Millipore filter paper to eliminate sodium chloride interferences. Several nonexposure calibration runs indicated that the loss of sulfur dioxide on the filter paper was negligible.

The concentration of sodium chloride aerosol was determined by withdrawing the exposure mixture at 21 liters/min for 20 minutes through HA Millipore paper, leaching the salt by filter immersion in distilled water, and analyzing by electrical conductivity. A calibration curve was prepared using reagent-grade sodium chloride. Because of the length of time required to sample for the sodium chloride aerosol, this was done at the end of the exposure periods. Several nonexposure checks and postexposure checks found the concentrations to be very consistent over a period of several hours, ie, 2.2 ± 0.08 mg/cu m (mean ± SD).

The particle size distribution of the aerosol was determined by first sampling with an oscillating thermal precipitator onto a carbon-coated glass coverslip. The carbon film was transferred to a 200-mesh electron microscope grid prior to obtaining photographs with an electron microscope. The particles were sized using a particle sizing unit. The particles were all smaller than 0.40μ by weight, the mean size and standard deviation were 0.25μ and ±0.001μ, respectively (Fig 2).

Table 1 is a summary of pollutant concentrations to which subjects were exposed in this study. Variations are due to operating characteristics of the generation apparatus. As experience with the unit increased, outward leaks, and other problems were eliminated and reproducibility of concentrations improved. These mixtures of aerosol and gaseous pollutant were generated to specifically simulate the urban milieu. The concentrations of SO_2 are slightly higher than those ever recorded in an acute air pollution episode (London, 1952). During that catastrophe, the concentration of particulate matter was 0.9 mg/cu m.

Results

The data (Table 2) shown represent the mean of six determinations of R_A and TGV in the body plethysmograph. Other parameters of pulmonary mechanics are derived. Pulmonary flow resistance data is presented as an average of inspiratory and expiratory flow resistances based on six to ten breaths.

When compared with individual or mean group controls, no significant increases in C_L and R_L were seen during quiet breathing or during hyperventilation, either after SO_2 alone, or after the SO_2-aerosol mixture. Similarly, no significant changes in R_A, airway conductance (G_A), or specific conductance could be demonstrated. Thoracic gas volume did not change significantly. These studies confirm those of Frank et al.[14] Mea-

Table 2.—*Effect of Exposures on Various Pulmonary Mechanics Measurements**

	Control	p 10 ft SO_2	p 30 ft SO_2	Control	p 10 ft Mix	p 30 ft Mix	Order
Individual data							
Subject 6							
R_L	0.41, 1.23	0.91, 1.40	0.90, 1.23	1.63, 1.80	1.56, 1.90	1.30, 1.87	
C_L	0.20, 0.21	0.28, 0.22	0.27, 0.25	0.27, 0.20	0.18, 0.18	0.22, 0.18	
R_A	0.70 —	0.97 —	0.95 —	1.00 —	0.96 —	0.95 —	Gas, Mix
G_A	1.42 —	1.03 —	1.05 —	1.00 —	1.04 —	1.05 —	
TGV	3.36 —	3.37 —	3.50 —	3.40 —	3.24 —	3.28 —	
G_A/TGV	0.42 —	0.31 —	0.30 —	0.29 —	0.32 —	0.32 —	
Subject 7							
R_L	2.02, 1.69	1.90, 1.80	1.33, 1.66	1.50 —	2.00, 1.90	1.80, 1.60	
C_L	0.25, 0.21	0.29, 0.26	0.27, 0.24	0.24 —	0.28, 0.30	0.35, 0.23	
R_A	1.12 —	1.18 —	1.03 —	1.10 —	0.98 —	1.08 —	
G_A	0.89 —	0.85 —	0.97 —	0.91 —	1.02 —	0.93 —	Gas, Mix
TGV	5.20 —	4.94 —	5.12 —	5.10 —	5.27 —	5.05 —	
G_A/TGV	0.17 —	0.17 —	0.19 —	0.18 —	0.19 —	0.18 —	
Subject 8							
R_L	1.70, 2.30	— —	1.05, 2.50	2.02 —	1.90, 2.30	2.00, 2.40	
C_L	0.21, 0.19	— —	0.18, 0.13	0.20 —	0.16, 0.18	0.16, 0.15	
R_A	1.04 —	1.11 —	1.25 —	1.02 —	1.23 —	1.13 —	
G_A	0.96 —	0.90 —	0.80 —	0.98 —	0.81 —	0.88 —	Gas, Mix
TGV	2.88 —	2.94 —	2.94 —	2.99 —	2.83 —	2.97 —	
G_A/TGV	0.33 —	0.31 —	0.27 —	0.33 —	0.29 —	0.30 —	
Subject 10							
R_L	1.84, 2.00	2.03, 2.90	1.70, 2.00	1.80, 2.00	1.70, 2.50	1.50, 2.10	
C_L	0.24, 0.21	0.31, 0.23	0.31, 0.30	0.32, 0.22	0.29, 0.22	0.26, 0.14	
R_A	1.25 —	1.40 —	1.09 —	1.15 —	1.08 —	1.12 —	Gas, Mix
G_A	0.80 —	0.71 —	0.92 —	0.87 —	0.93 —	0.89 —	
TGV	5.28 —	5.08 —	5.38 —	4.87 —	5.25 —	5.16 —	
G_A/TGV	0.15 —	0.14 —	0.17 —	0.18 —	0.18 —	0.17 —	
Subject 9							
R_L	1.60, 3.30	2.70, 2.80	1.40, 1.70	1.40, 1.80	1.90, 1.80	1.60, 1.50	
C_L	0.27, 0.25	0.30, 0.30	0.36, 0.23	0.25, 0.31	0.27, 0.32	0.30, 0.25	
R_A	1.04 —	1.05 —	1.04 —	1.03 —	0.97 —	1.02 —	Gas, Mix
G_A	0.96 —	0.95 —	0.96 —	0.97 —	1.03 —	0.98 —	
TGV	4.48 —	4.58 —	4.50 —	4.65 —	4.82 —	4.84 —	
G_A/TGV	0.21 —	0.21 —	0.21 —	0.21 —	0.21 —	0.20 —	
Subject 1							
R_L	1.04, 1.25	1.20, 1.10	1.50, 1.70	1.20, 1.60	1.20, 1.70	0.96, 1.80	
C_L	0.39, 0.63	0.36, 0.63	0.26, 0.23	0.28, 0.30	0.30 —	0.23, 0.25	
R_A	0.69 —	0.74 —	0.64 —	0.66 —	0.85 —	0.70 —	Gas, Mix
G_A	1.45 —	1.35 —	1.56 —	1.52 —	1.18 —	1.43 —	
TGV	4.40 —	4.20 —	4.35 —	3.97 —	4.16 —	3.90 —	
G_A/TGV	0.33 —	0.32 —	0.36 —	0.38 —	0.28 —	0.37 —	
Subject 2							
R_L	1.80 —	1.60, 1.50	1.40, 1.50	2.60, 2.40	2.10, 1.40	1.50, 1.60	
C_L	0.25 —	0.29, 0.28	0.37, 0.42	0.36, 0.37	0.30, 0.52	0.29, 0.40	
R_A	1.59 —	1.65 —	1.61 —	1.57 —	1.62 —	1.55 —	Mix, Gas
G_A	0.63 —	0.61 —	0.62 —	0.64 —	0.62 —	0.65 —	
TGV	5.68 —	5.74 —	5.54 —	6.26 —	5.54 —	5.64 —	
G_A/TGV	0.11 —	0.11 —	0.11 —	0.10 —	0.11 —	0.12 —	
Subject 3							
R_L	0.99, 2.00	1.40, 1.90	1.50, 1.90	0.83, 1.30	1.80, 2.10	1.30, 2.00	
C_L	0.24, 0.29	0.27, 0.25	0.27, 0.26	0.22, 0.22	0.27, 0.23	0.28, 0.27	
R_A	1.05 —	1.20 —	1.45 —	1.32 —	1.56 —	1.42 —	Mix, Gas
G_A	0.95 —	0.83 —	0.69 —	0.76 —	0.64 —	0.70 —	
TGV	3.78 —	3.68 —	3.35 —	3.44 —	3.18 —	3.38 —	
G_A/TGV	0.25 —	0.23 —	0.21 —	0.22 —	0.20 —	0.21 —	
Subject 5							
R_L	1.41, 1.55	1.10, 1.71	1.78, 1.71	2.36, 2.37	1.93, 1.62	1.41, 1.55	
C_L	0.27, 0.25	0.25, 0.18	0.23, 0.26	0.15, 0.14	0.18, 0.23	0.27, 0.25	
R_A	1.42 —	1.47 —	1.42 —	1.42 —	1.47 —	1.38 —	
G_A	0.70 —	0.68 —	0.70 —	0.70 —	0.68 —	0.72 —	Mix, Gas
TGV	4.85 —	4.55 —	4.61 —	4.73 —	4.62 —	4.85 —	
G_A/TGV	0.14 —	0.15 —	0.15 —	0.15 —	0.15 —	0.15 —	
Subject 4							
R_L	1.97, 2.09	1.89, 2.12	1.89, 2.30	1.82, 1.61	1.47, 2.05	2.28, 2.01	
C_L	0.16, 0.15	0.15, 0.13	0.16, 0.15	0.15, 0.14	0.15, 0.13	0.15, 0.13	
R_A	1.97 —	2.05 —	2.06 —	1.67 —	2.00 —	1.83 —	Mix, Gas
G_A	0.51 —	0.49 —	0.48 —	0.60 —	0.50 —	0.55 —	
TGV	2.85 —	2.76 —	2.78 —	3.00 —	2.73 —	2.89 —	
G_A/TGV	0.18 —	0.18 —	0.17 —	0.20 —	0.18 —	0.19 —	

Table 2.—*Effect of Exposures on Various Pulmonary Mechanics Measurements*—(Continued)*

	Control	p 10 ft SO_2	p 30 ft SO_2	Control	p 10 ft Mix	p 30 ft Mix	Order
Grouped data							
R_L	1.48, 1.93	1.64, 1.92	1.44, 1.82	1.72, 1.86	1.76, 1.93	1.57, 1.84	
C_L	0.25, 0.27	0.28, 0.28	0.27, 0.25	0.24, 0.24	0.24, 0.26	0.25, 0.23	
R_A	1.19 —	1.28 —	1.25 —	1.19 —	1.27 —	1.22 —	—
G_A	0.84 —	0.88 —	0.88 —	0.90 —	0.85 —	0.88 —	
TGV	4.27 —	4.18 —	4.21 —	4.24 —	4.16 —	4.20 —	
G_A/TGV	0.23 —	0.21 —	0.21 —	0.22 —	0.21 —	0.22 —	

* R_L, cm H_2O/liter/sec; C_L, liter per centimeter H_2O; R_A, cm H_2O/liter/sec; G_A, 1/R_A; TGV, liters; and G_A/TGV (specific conductance), sec^{-1} cm H_2O^{-1}.

surements of R_L and C_L during rapid breathing were also unaffected by any exposure.

Figures 3 to 5 illustrate the absence of significant change in group mean values of R_L, C_L, or G_A per TGV following any exposure condition. The R_L and C_L data seemed to add little to the results, for they follow the same trends as the more simply obtained body plethysmograph data.

The wide scatter of individual values and the lack of significant trend can be seen in Table 2 and 3, and Fig 6 to 8. One or two possible "hyperreactors" can be identified here. Control values are all within reported normal ranges for these measurements.

Table 3.—*Effects of Exposures on Lung Resistance and Specific Airway Conductance*

		% Change vs Control					
Subject		R_L*	G_A/TGV*	Subject		R_L	G_A/TGV
6	$\bar{p}$ 10' SO_2	+122.2	−26.2	1	$\bar{p}$ 10' SO_2	+ 15.3	− 3.0
	$\bar{p}$ 30' SO_2	+119.5	−28.6		$\bar{p}$ 30' SO_2	+ 44.2	+ 9.0
	$\bar{p}$ 10' Mix	− 4.7	+10.3		$\bar{p}$ 10' Mix	0.0	−26.3
	$\bar{p}$ 30' Mix	− 20.2	+10.3		$\bar{p}$ 30' Mix	− 20.0	− 2.7
7	$\bar{p}$ 10' SO_2	− 6.0	0.0	2	$\bar{p}$ 10' SO_2	− 11.1	0.0
	$\bar{p}$ 30' SO_2	− 34.2	+11.7		$\bar{p}$ 30' SO_2	− 22.2	0.
	$\bar{p}$ 10' Mix	+ 33.3	+ 9.5		$\bar{p}$ 10' Mix	− 19.2	+10.0
	$\bar{p}$ 30' Mix	+ 20.0	0.0		$\bar{p}$ 30' Mix	− 42.3	+20.0
8	$\bar{p}$ 10' SO_2	—	− 6.0	3	$\bar{p}$ 10' SO_2	+ 41.4	− 8.0
	$\bar{p}$ 30' SO_2	− 38.2	− 8.2		$\bar{p}$ 30' SO_2	+ 51.5	−16.0
	$\bar{p}$ 10' Mix	− 5.9	−12.1		$\bar{p}$ 10' Mix	+116.9	− 9.1
	$\bar{p}$ 30' Mix	− 1.0	− 9.0		$\bar{p}$ 30' Mix	+ 56.6	− 4.5
10	$\bar{p}$ 10' SO_2	+ 10.3	− 6.7	5	$\bar{p}$ 10' SO_2	− 22.0	+ 7.1
	$\bar{p}$ 30' SO_2	− 7.6	+13.3		$\bar{p}$ 30' SO_2	+ 26.2	+ 7.1
	$\bar{p}$ 10' Mix	− 5.6	0.0		$\bar{p}$ 10' Mix	− 18.2	0.0
	$\bar{p}$ 30' Mix	− 16.7	− 5.5		$\bar{p}$ 30' Mix	− 40.3	0.0
9	$\bar{p}$ 10' SO_2	+ 68.8	0.0	4	$\bar{p}$ 10' SO_2	− 4.1	0.0
	$\bar{p}$ 30' SO_2	− 12.5	0.0		$\bar{p}$ 30' SO_2	− 4.1	− 5.6
	$\bar{p}$ 10' Mix	+ 35.7	0.0		$\bar{p}$ 10' Mix	− 19.2	−10.0
	$\bar{p}$ 30' Mix	+ 14.3	− 4.8		$\bar{p}$ 30' Mix	+ 25.3	− 5.2

* R_L, cm H_2O/liter/sec; G_A/TGV, sec^{-1} cm H_2O^{-1}.

Except for subject 10, who complained of some dryness of the throat, there were no subjective symptoms associated with any exposure.

Comment

This study confirms existing evidence[6,14,15] that human exposures to low concentrations (< 3.0 ppm) of SO_2 in air do not result in immediate physiologic effects on measures of pulmonary mechanics. Wide subject variability, and hour-to-hour variation in airway resistance and conductance[16] made detection and interpretation of small transient changes difficult. Furthermore, time-series analysis studies in New York[17] and Tennessee[18] have demonstrated a 1 to 2 day lag between peak ambient levels of SO_2 and development of cough or worsening of asthma. Spicer[16] has confirmed this relationship in Baltimore, using a sophisticated statistical analysis of changing SO_2 concentrations and measurements of pulmonary airway conductance and resistance as a function of time (a so-called power spectrum analysis). Such work suggests that the expected effects of low-concentration SO_2 exposures are delayed unless pulmonary defense mechanisms are in some other way altered.

Inhaled aerosols may yet be shown to act in this fashion, in some way altering the immediate adaptive mechanisms of the airways and lung, rendering them more susceptible to otherwise ineffective concentrations of gaseous pollutant. Stokinger[19] and Anderson[20] have recently discussed the potential of gas-aerosol interaction, and the limitations of testing adequately for its presence or absence. It is unclear whether or not

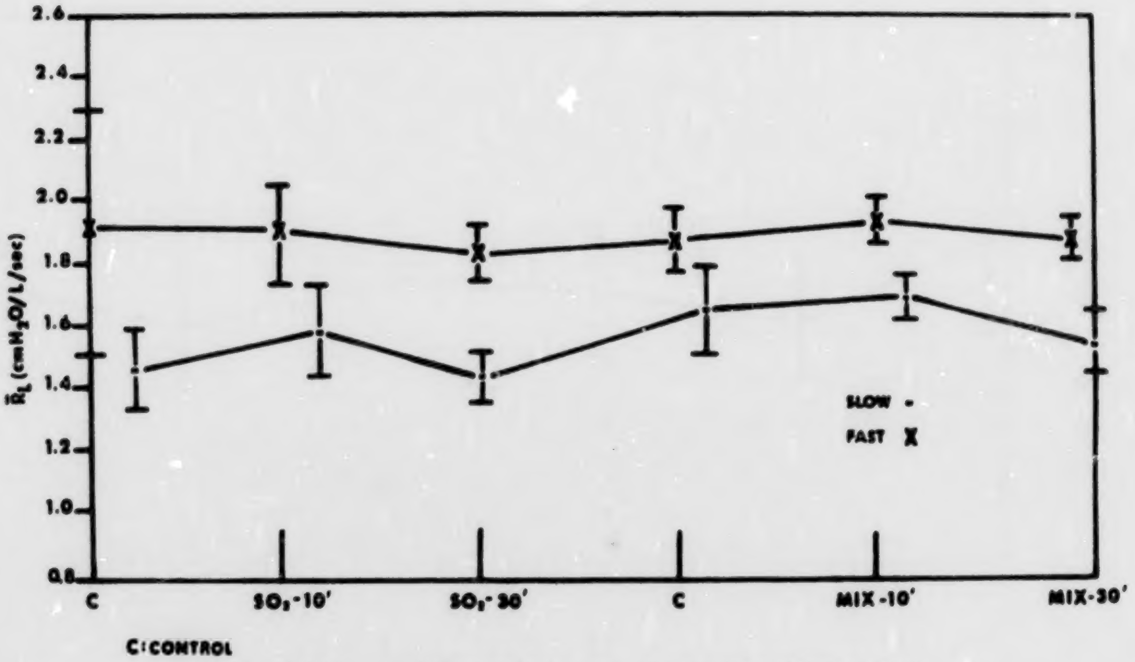
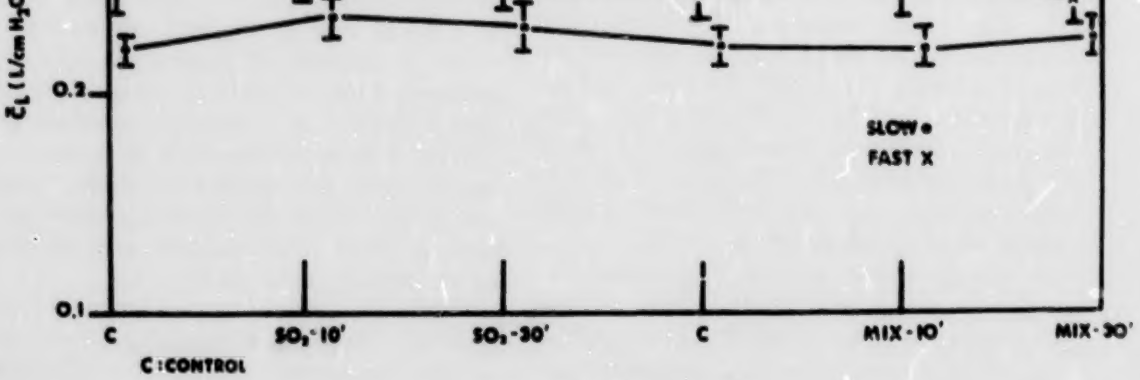


Fig 3.—Total lung resistance (R_L) changes after exposure (grouped data).

Fig 4.—Lung compliance (C_L) changes after exposure (grouped data).



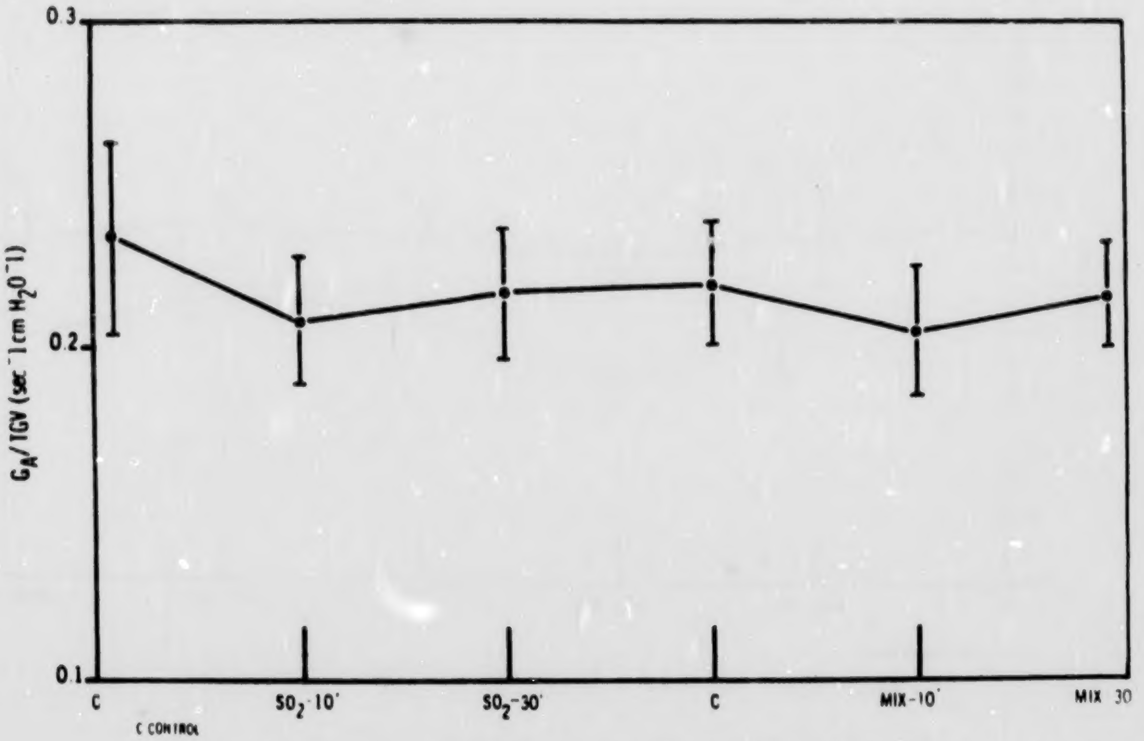


Fig 5.—Specific airway conductance changes after exposure (grouped data).

the aerosols in themselves need to be "irritant" to produce an effect in man, though they need not be in animals. Toyama's industrial dusts may have been more irritant than the NaCl aerosol of Frank et al[6] and our own, and this may account in part for the evocation of response from his SO_2-dust exposed subjects.

We were able to identify at least one possible "hyperreactor" to SO_2 in the present study (subject 3, a 24-year-old nonsmoker). Our work suggests, as have other studies,[14,15] that there may be only one or two physiologic "reactors" for every ten exposed subjects. The implication for future exposure studies is that large numbers of "normal" subjects will need to be studied to locate persons who show effects of inhaled pollutants on pulmonary mechanics.

A study which probed immediate gas-aerosol synergism in patients already affected by pulmonary disease might report positive results where ours have been negative. Support for this exists in the literature,[21] though complete aerosol characterization data are not given. Medicolegal and ethical considerations make studies of this kind difficult.

Conclusions

In summary, like Frank et al[6] and the work recently reported by Snell and Luchsinger,[22] we could not demonstrate gas-aerosol synergism for SO_2 and inert aerosols at concentrations which approximate those in urban atmospheres. These experiments suggest that grouped population data may not be as sensitive an indicator of effect in the experimental exposure situation as they are in the epidemiological setting. These findings in humans are in marked contrast to the study in animals of Amdur et al,[4,5] where grouped data, as well as single responses, gave evidence of a synergistic effect when guinea pigs were exposed to mixtures of aerosol and gas similar to those reported here. (She used the same indicator of response, namely pulmonary flow resistance, in her studies as we did.)

While gas-aerosol synergism may yet be proven an important toxicologic mechanism in man, we suspect that reactor, characteristics of reactant, and timing and sensitivity of measurement will have to be more carefully considered in future studies if such an effect is to be demonstrated.

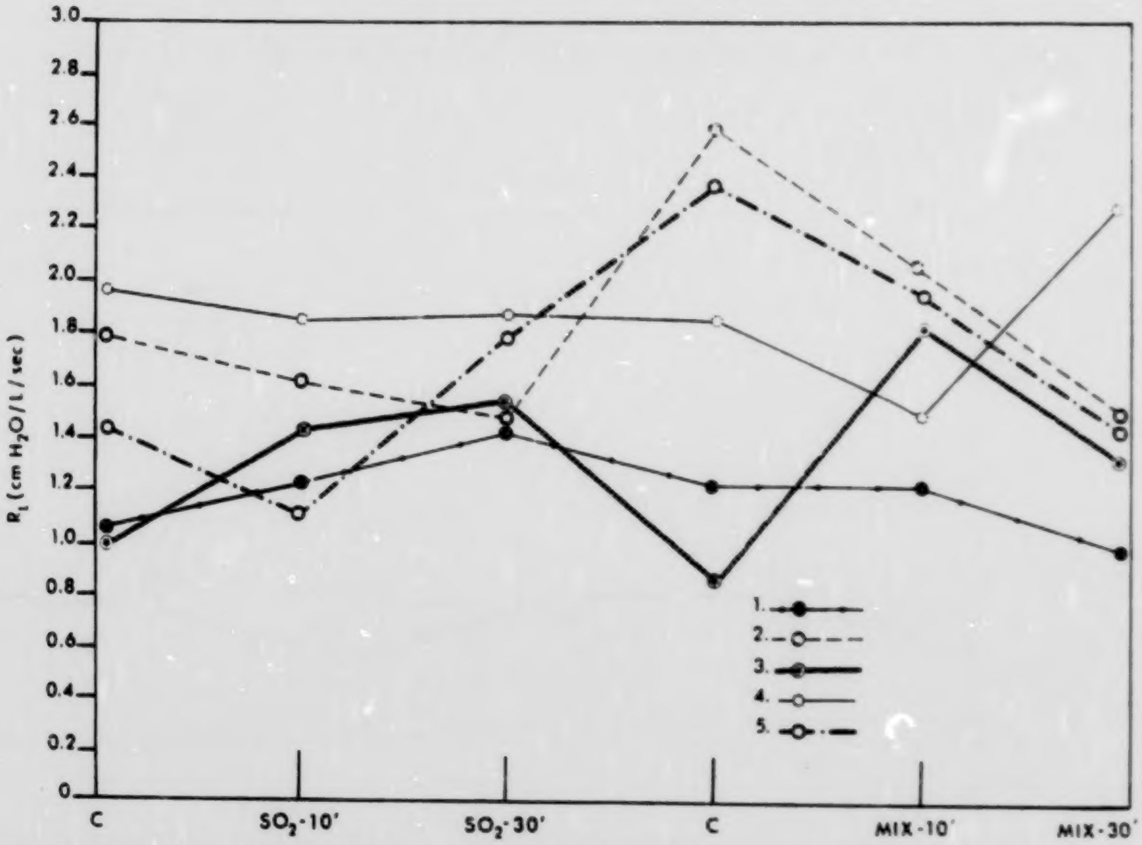
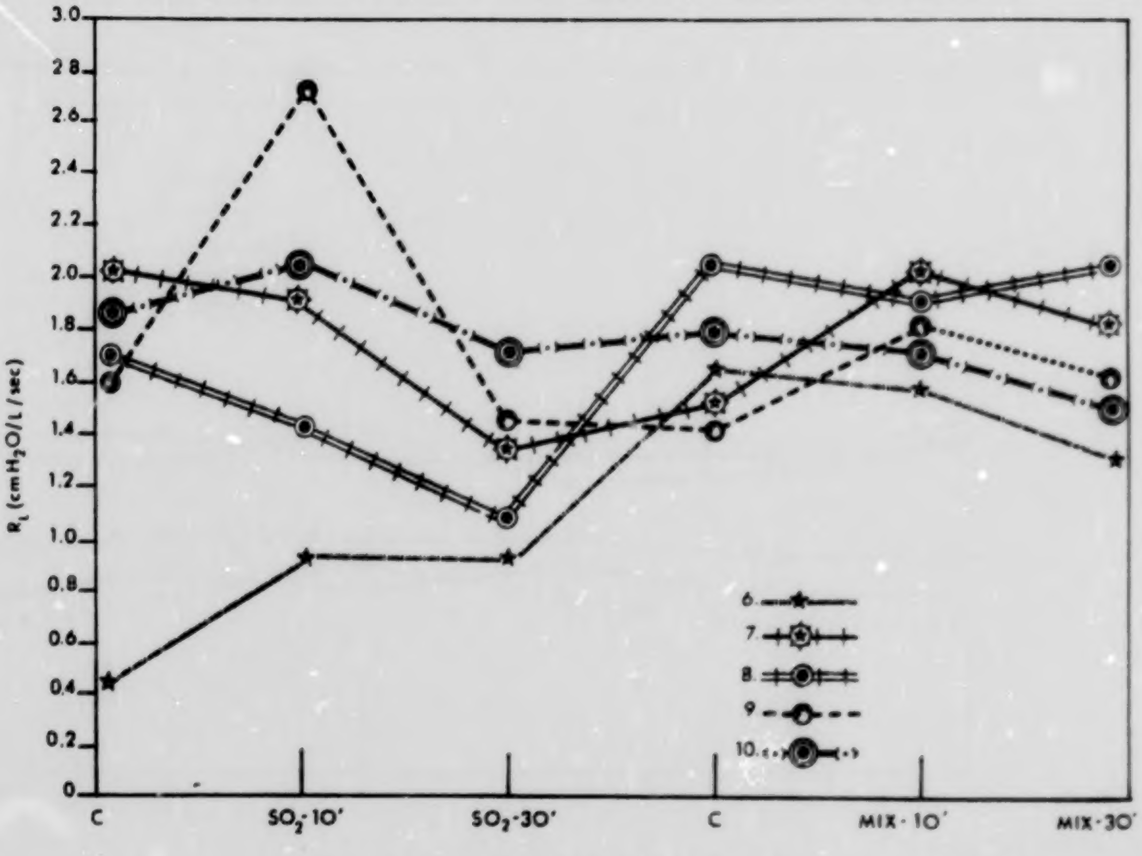


Fig 6.—Plot of lung resistance changes in individual subjects after exposure to SO_2 gas and NaCl aerosol.



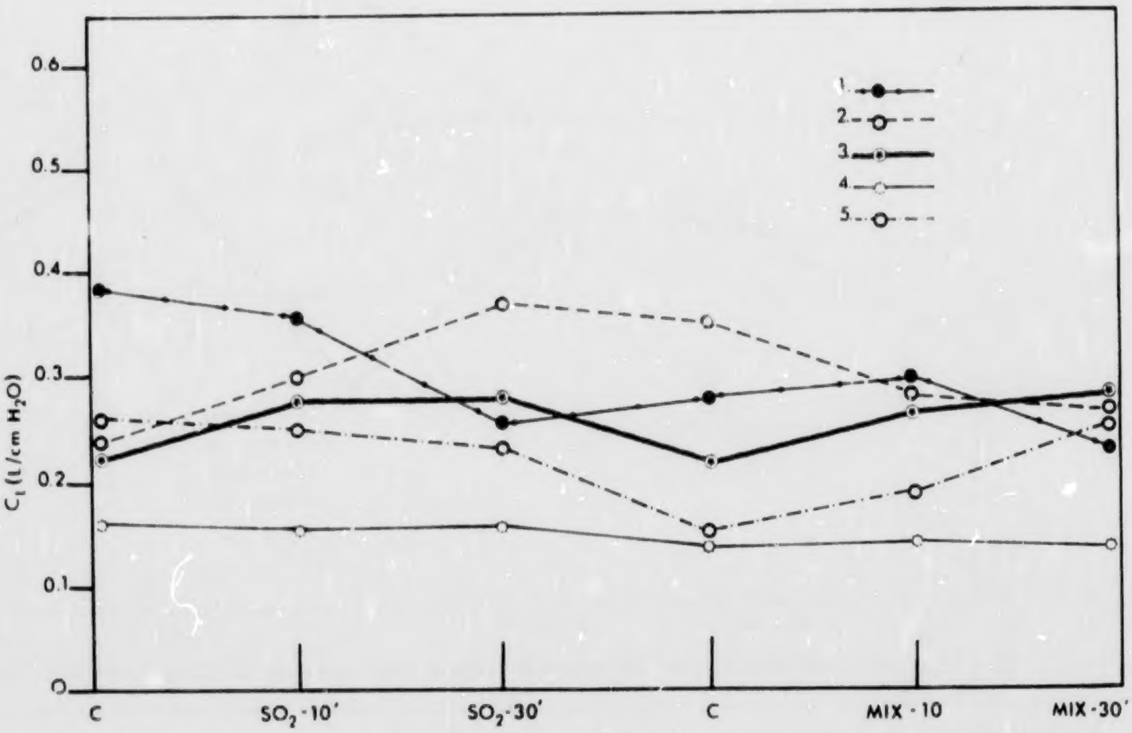
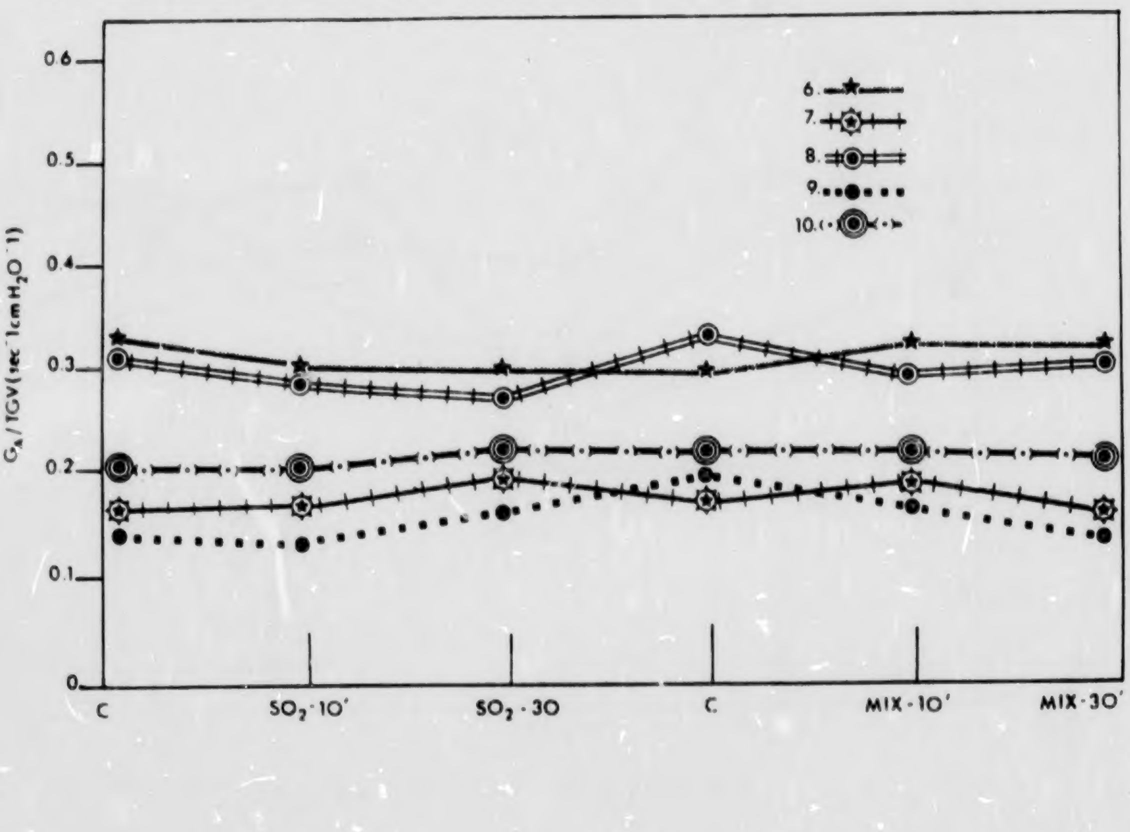


Fig 7.—Plot of lung compliance changes in individual subjects after exposure to SO_2 gas and NaCl aerosol.



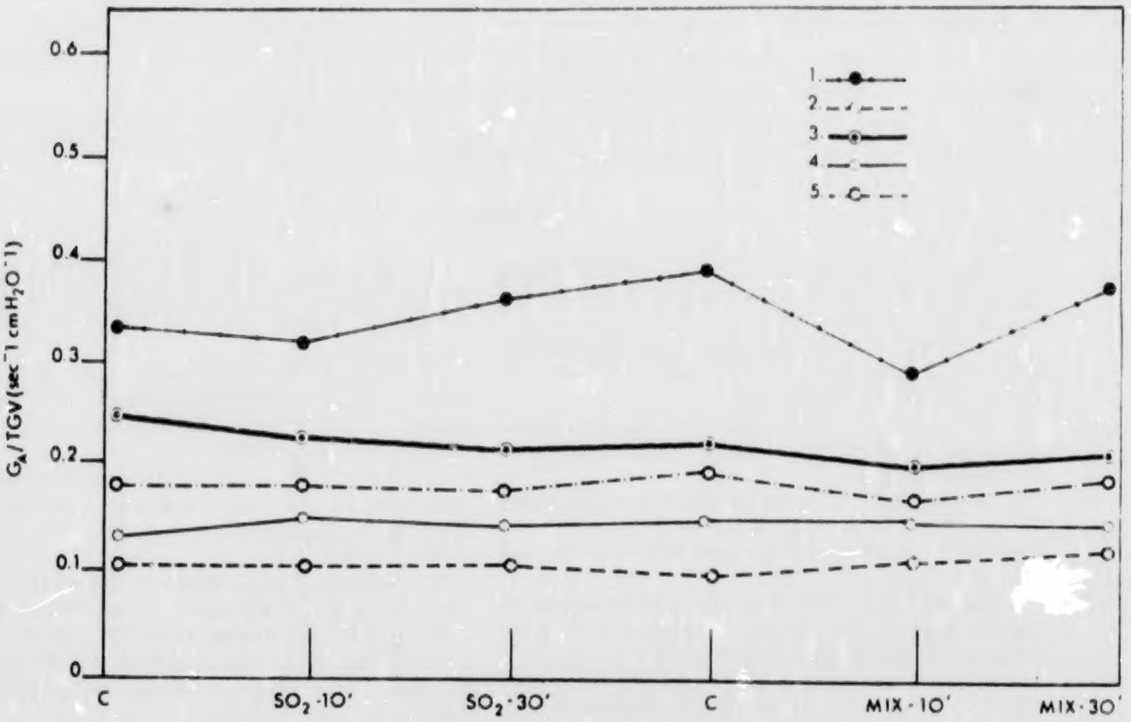
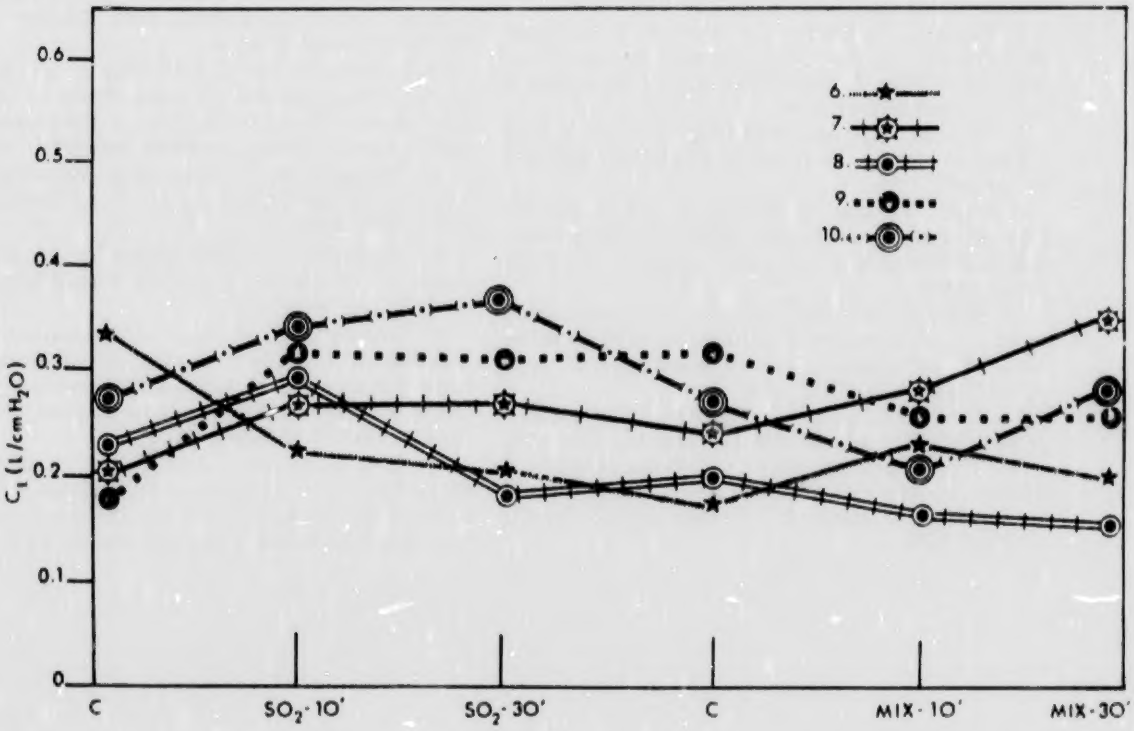


Fig 8.—Plot of specific airway conductance in individual subjects after exposure to SO_2 gas and NaC1 aerosol.



Resting pulmonary mechanics studies may not represent the best approach to problems of acute-effect air pollution toxicology in man. Studies of distribution of ventilation or changes in pulmonary mechanics following exposure during exercise may possibly be more sensitive indicators of response.

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TABLE 5

Cat No. 1676

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

	Pulmonary Flow Resistance [(b)]														
	Control	Mech. Stim.	% Change	Control	Low SO_2	% Change	Control	Mech. Stim.	% Change	Control	SO_2 & NaCl	% Change	Control	Mech. Stim.	% Change
	9.5	68.2	617.9	8.4	9.5	0	9.5	59.7	528.4	14.0	15.2	60	10.6	72.8	586.8
	9.5			9.5	10.6	11.6				10.6	16.3	71.6			
				9.5	12.9	35.8				9.5	15.2	60			
Mean±	9.5	68.2		9.1	11.0		9.5	59.7		11.4	15.6		10.6	72.8	
S.D.	0			0.6	1.7					2.3	0.6				
	REFLEX INTACT			Δ N.S.			REFLEX INTACT			Δ N.S.			REFLEX INTACT		
	Lung Compliance [(c)]														
	Control	Mech. Stim.	% Change	Control	Low SO_2	% Change	Control	Mech. Stim.	% Change	Control	SO_2 & NaCl	% Change	Control	Mech. Stim.	Change
	14.5	3.8	-73.8	15.0	12.8	-13.7	13.2	3.4	-74.2	13.6	11.4	-13.6	12.1	8.3	-31.4
	14.5			15.0	12.4	-16.4				13.2	11.4	-13.6			
				14.5	12.8	-13.0				12.8	11.4	-13.6			
Mean±	14.5	3.8		14.8	12.7		13.2	3.4		13.2	11.4		12.1	8.3	
S.D.	0			0.3	0.2					0.4	0				
				P<0.01						P<0.05					
Sequence of Challenge [(a)]	(1)			(2)			(3)			(4)			(5)		

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm H_2O/1/sec.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

TABLE 5 (Continued)

Cat No. 1676

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

	Pulmonary Flow Resistance [b]												
	Control	NaCl	% Change	Control	Mech. Stim.	% Change	Control	High SO_2	% Change	Control	Mech. Stim.	% Change	
	9.5	12.9	35.9	9.5	98.6	937.9	9.5	10.6	11.6	9.5	86.3	808.4	
	9.5	14.0	47.4				9.5	12.9	35.08				
		12.9	35.8				9.5	12.9	35.8				
Mean±	9.5	13.3		9.5	98.6		9.5	12.1		9.5	86.3		
S.D.	0	0.6					0	1.3					
		P<0.01			REFLEX INTACT			Δ N.S.			REFLEX INTACT		
	Lung Compliance [c]												
	Control	NaCl	% Change	Control	Mech. Stim.	% Change	Control	High SO_2	% Change	Control	Mech. Stim.	% Change	
	12.4	11.4	-6.9	11.7	4.1	-65	11.4	16.2	42.1	16.2	4.7	-71	
	12.1	11.1	-9.4				11.4	16.2	42.1				
		11.4	-6.9				11.4	16.2	42.1				
Mean±	12.3	11.3		11.7	4.1		11.4	16.2		16.2	4.7		
S.D.	0.2	0.2					0	0					
		P< 0.05						P 0.01					
Sequence of Challenge [a]	(6)			(7)			(8)			(9)			

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm H_2O/1/sec.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

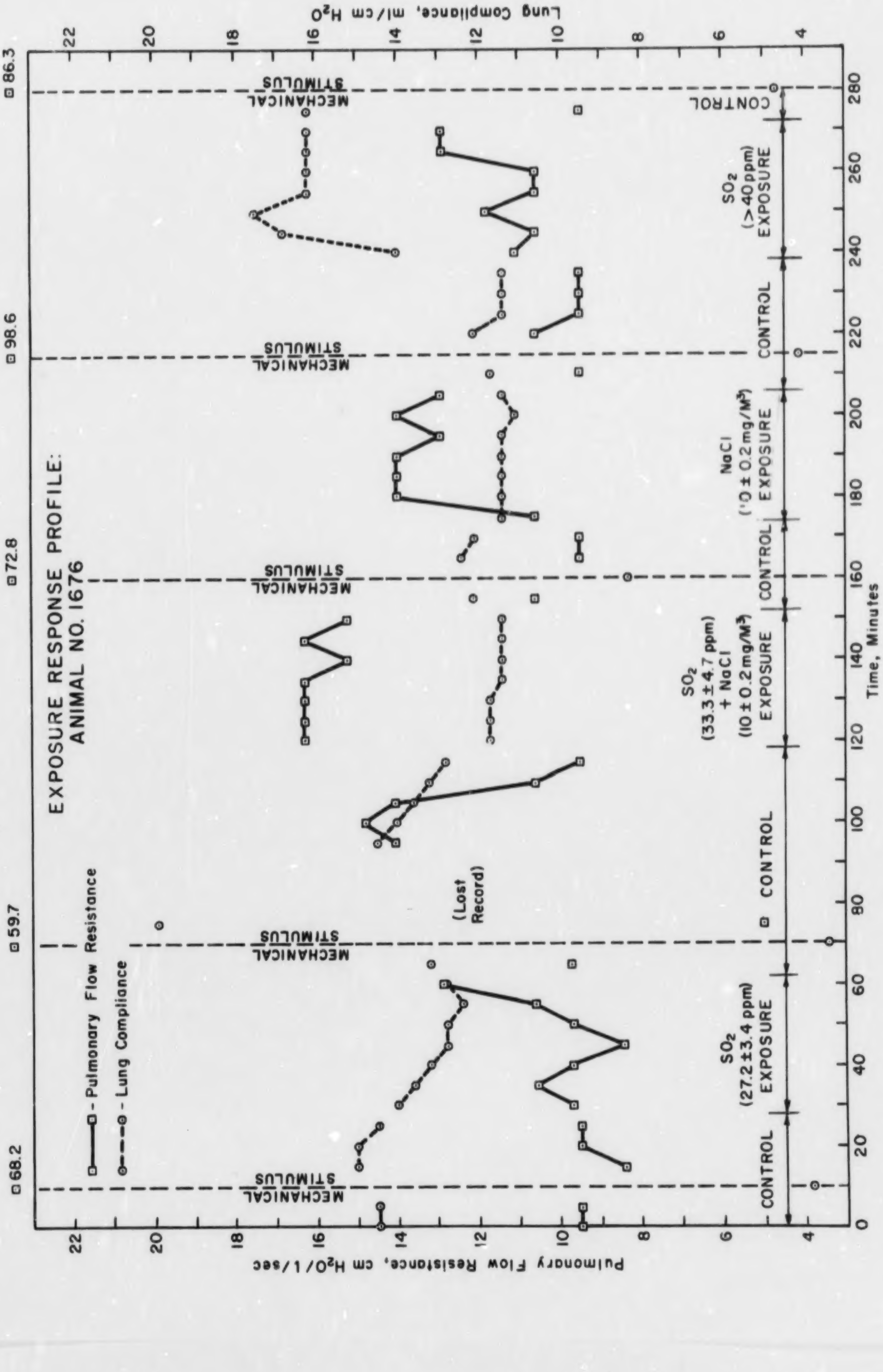

EXPOSURE RESPONSE PROFILE:
ANIMAL NO. 1676
- Pulmonary Flow Resistance
- Lung Compliance
Pulmonary Flow Resistance, cm H_2O/1/sec
Lung Compliance, ml/cm H_2O
Time, Minutes
0
20
40
60
80
100
120
140
160
180
200
220
240
260
280
4
6
8
10
12
14
16
18
20
22
68.2
59.7
72.8
98.6
86.3
MECHANICAL STIMULUS
MECHANICAL STIMULUS
MECHANICAL STIMULUS
MECHANICAL STIMULUS
MECHANICAL STIMULUS
(Lost Record)
CONTROL
CONTROL
SO_2 (27.2 ± 3.4 ppm) EXPOSURE
CONTROL
CONTROL
SO_2 (33.3 ± 4.7 ppm) + NaCl (10 ± 0.2 mg/M³) EXPOSURE
CONTROL
NaCl (10 ± 0.2 mg/M³) EXPOSURE
CONTROL
SO_2 (>40 ppm) EXPOSURE
CONTROL

TABLE 6

Cat No. 1651

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

	Pulmonary Flow Resistance (b)														
	Control	Mech. Stim.	% Change	Control	Low SO_2	% Change	Control	Mech. Stim.	% Change	Control	SO_2+ NaCl	% Change	Control	Mech. Stim.	% Change
	14.5	54.4	275.2	14.5	11.9	-18.6	14.5	163.9	1030	14.5	13.0	-10.3	10.5	84.1	572.8
	14.5			14.5	13.0	-10.3				14.5	14.5	0	14.5		
				14.5	11.8	-18.6				14.5	13.0	-10.3			
Mean±	14.5	54.4		14.5	12.2		14.5	163.9		14.5	13.5		12.5	84.1	
S.D.	0			0	0.7					0	0.9		2.8		
	REFLEX INTACT			$P<0.05$			REFLEX INTACT			Δ N.S.			REFLEX INTACT		
	Lung Compliance (c)														
	Control	Mech. Stim.	% Change	Control	Low SO_2	% Change	Control	Mech. Stim.	% Change	Control	SO_2+ NaCl	% Change	Control	Mech. Stim.	% Change
	11.1	7.2	-35.1	10.5	14.1	30.6	14.1	5.3	-62.4	12.4	15.7	28.7	16.3	5.2	-67.5
	11.1			10.8	13.6	25.9				12.1	14.1	15.6	15.7		
				11.1	13.6	25.9				12.1	15.1	23.8			
Mean±	11.1	7.2		10.8	13.8		14.1	5.3		12.2	15.0		16.0	5.2	
S.D.	0			0.3						0.2	0.8		0.4		
				$P<0.01$						$P<0.05$					
Sequence of Challenge (a)	(1)			(2)			(3)			(4)			(5)		

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm H_2O/1/sec.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

TABLE 6 (Continued)

Cat No. 1651

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

Pulmonary Flow Resistance (b)													
	Control	NaCl	% Change	Control	Mech. Stim.	% Change	Control	High SO_2	% Change	Control	Mech. Stim.	% Change	
	13.1	11.7	-19.3	11.8	151.1	1267.4	14.5	19.3	35.1	9.3	119	1179.6	
	14.5	11.7	-19.3	10.3			14.5	22.9	57.9				
		11.8	-18.6					19.3	33.1				
Mean±	13.8	11.7		11.1	151.1		14.5	20.5		9.3	119		
S.D.	1.0	0.1		1.1			0	2.1					
		N.S.			REFLEX INTACT			$P< 0.05$			REFLEX INTACT		
Lung Compliance (c)													
	Control	NaCl	% Change	Control	Stim.	Change	Control	SO_2	Change	Control	Mech. Stim.	% Change	
	14.1	15.1	5.2	15.1	3.9	-74.4	13.6	15.7	13.4	15.7	4.9	-68.8	
	14.6	15.1	5.2	14.6			14.1	15.7	13.4				
		15.1	5.2					15.7	13.4				
Mean±	14.4	15.1		14.9	3.9		13.9	15.7		15.7	4.9		
S.D.	0.4	0		0.4			0.4	0					
		N.S.						Δ N.S.					
Sequence of Challenge (a)		(6)			(7)			(8)			(9)		

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm H_2O/1/sec.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

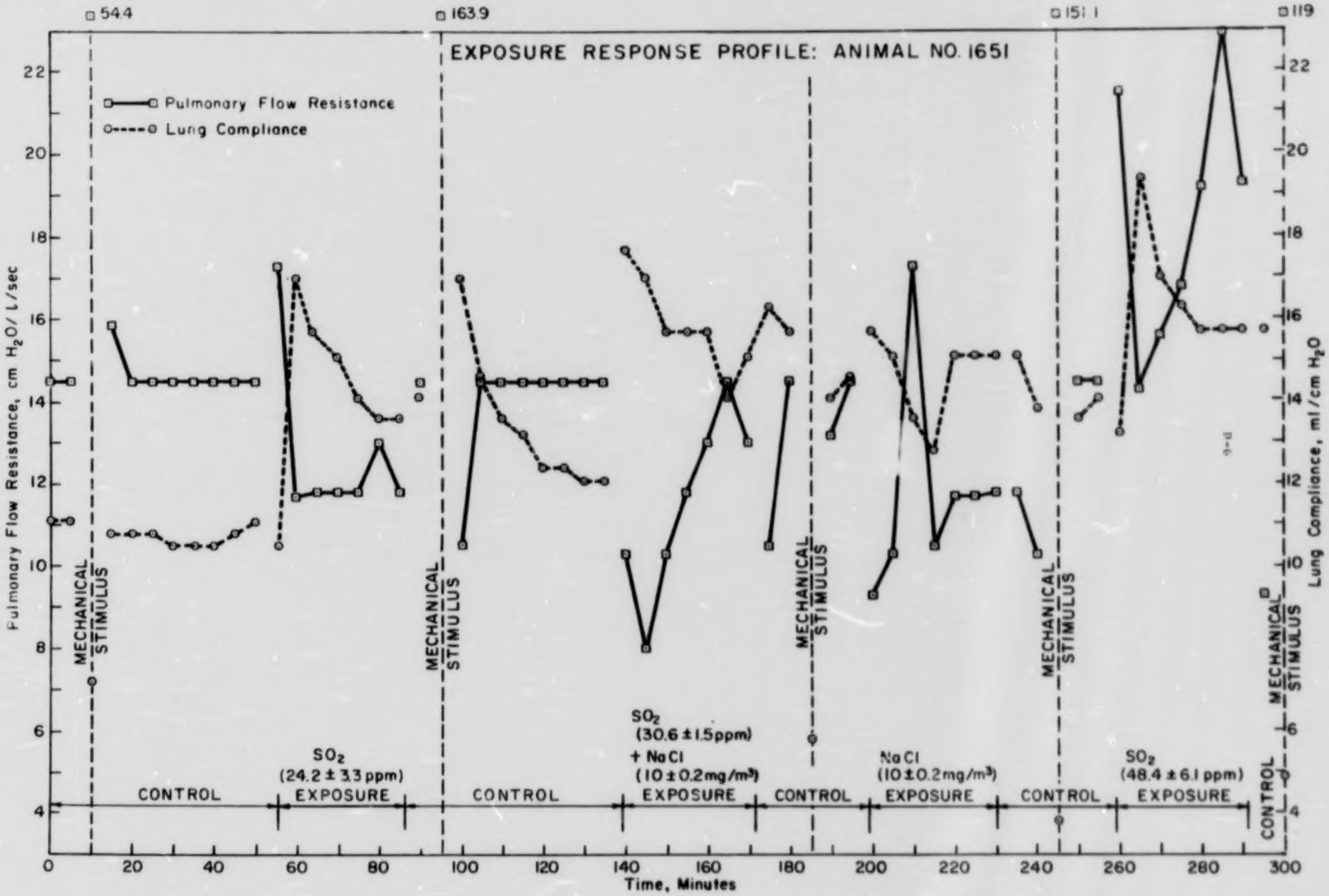

EXPOSURE RESPONSE PROFILE: ANIMAL NO. 1651
Pulmonary Flow Resistance
Lung Compliance
Pulmonary Flow Resistance, cm H_2O/ L/sec
Lung Compliance, ml/cm H_2O
Time, Minutes
54.4
163.9
151.1
119
MECHANICAL STIMULUS
MECHANICAL STIMULUS
MECHANICAL STIMULUS
MECHANICAL STIMULUS
MECHANICAL STIMULUS
CONTROL
SO_2 (24.2 ± 3.3 ppm) EXPOSURE
CONTROL
SO_2 (30.6 ± 1.5ppm) + NaCl (10 ± 0.2mg/m³) EXPOSURE
CONTROL
NaCl (10 ± 0.2mg/m³) EXPOSURE
CONTROL
SO_2 (48.4 ± 6.1 ppm) EXPOSURE
CONTROL
0
20
40
60
80
100
120
140
160
180
200
220
240
260
280
300
4
6
8
10
12
14
16
18
20
22

TABLE 7

Cat No. 1612

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

	Control	Mech. Stim.	% Change	Control	Low SO_2	% Change	Control	Mech. Stim.	% Change	Control	SO_2+ NaCl	% Change	Control	Mech. Stim.	% Change
Pulmonary Flow Resistance (b)															
	20.9	156	646.4	20.9	27.1	29.7	28.1	103	329.2	20.9	29.2	39.7	20.9	119	469.4
	20.9			20.9	28.1	34.4	23			20.9	25.6	22.5			
				20.9	30.2	44.5	20.9				27.1	29.7			
Mean±	20.9	156		20.9	28.5		24.0	103		20.9	27.3		20.9	119	
S.D.	0			0	1.6		3.7			0	1.8				
	REFLEX INTACT			+0.05			REFLEX INTACT			P<0.05			REFLEX INTACT		
Lung Compliance (c)															
	6.3	5.0	-21.3	7.0	6.5	-8.5	6.9	6.9	0	7.4	7.1	-1.4	7.7	7.7	0
	6.4			7.1	6.6	-7.0	7.0			7.0	8.4	16.7			
				7.1	6.4	-9.9	6.9				7.1	-1.4			
Mean±	6.3			7.1	6.5		6.9	6.9		7.2	7.5		7.7	7.7	
S.D.	0.1			0.1	0.1		0.1			0.3	0.6				
				P<0.01						Δ N.S.					
Sequence of Challenge (a)	(1)			(2)			(3)			(4)			(5)		

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm H_2O/1/sec.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

TABLE 7 (Continued)

Cat No. 1612

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

	Control	NaCl	% Change	Control	Mech. Stim.	% Change	Control	High SO_2	% Change	Control	Mech. Stim.	% Change	
Pulmonary Flow Resistance [(b)]													
	20.9	38.7	85.2	20.9	81.6	290.4	20.9	28.1	34.4	20.9	134	54.1	
	20.9	30	43.5				20.9	27.1	29.7				
		33.9	62.2				23	32.2	54.1				
Mean±	20.9	34.2		20.9	81.6		21.6	29.1		20.9	134		
S.D.	0	4.4					1.2	2.7					
	P< 0.05			REFLEX INTACT			P< 0.05			REFLEX INTACT			
Lung Compliance [(c)]													
	7.7	9.3	9.2	8.8	6.7	-23.9	7.7	6.4	-13.1	7.1	5.0	-29.6	
	7.5	9.4	10.5				6.5	8.4	14.0				
		9.1	6.6				7.9	6.1	-17.2				
Mean±	7.6	9.3		8.8	6.7		7.4	7.0		7.1	5.0		
S.D.	0.1	0.2					0.8	1.3					
	P<0.01						Δ N.S.						
Sequence of Challenge [(a)]	(6)			(7)			(8)			(9)			

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm H_2O/1/sec.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

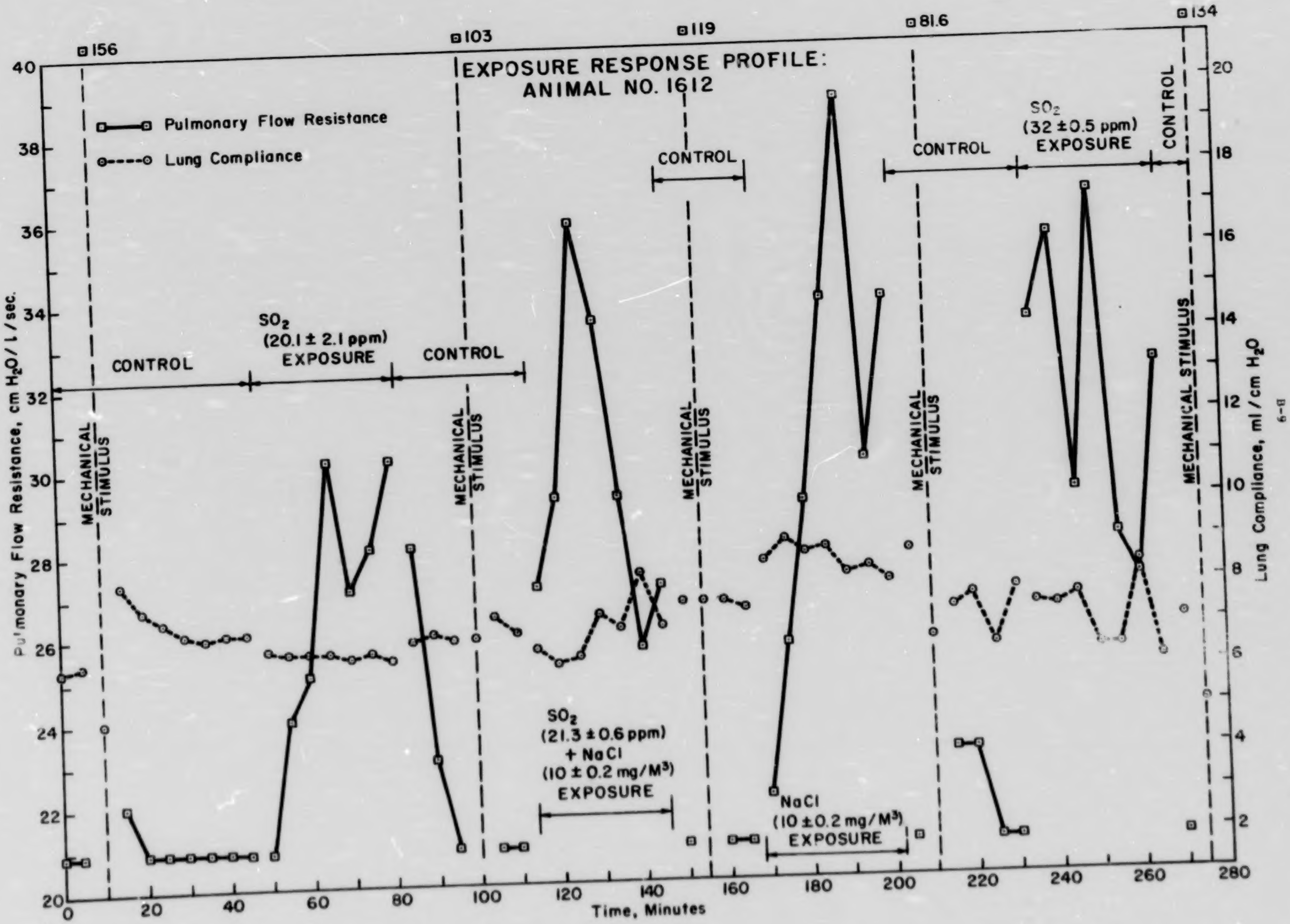

EXPOSURE RESPONSE PROFILE:
ANIMAL NO. 1612
Pulmonary Flow Resistance
Lung Compliance
Pulmonary Flow Resistance, cm H_2O/l/sec.
Lung Compliance, ml/cm H_2O
Time, Minutes
156
103
119
81.6
134
MECHANICAL STIMULUS
MECHANICAL STIMULUS
MECHANICAL STIMULUS
MECHANICAL STIMULUS
MECHANICAL STIMULUS
CONTROL
SO_2 (20.1 ± 2.1 ppm) EXPOSURE
CONTROL
SO_2 (21.3 ± 0.6 ppm) + NaCl (10 ± 0.2 mg/M^3) EXPOSURE
CONTROL
NaCl (10 ± 0.2 mg/M^3) EXPOSURE
CONTROL
SO_2 (32 ± 0.5 ppm) EXPOSURE
CONTROL
20
22
24
26
28
30
32
34
36
38
40
0
20
40
60
80
100
120
140
160
180
200
220
240
260
280
2
4
6
8
10
12
14
16
18
20

TABLE 8

Cat No. 1633

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

	Pulmonary Flow Resistance (b)														
	Control	Mech. Stim.	% Change	Control	Low SO_2	% Change	Control	Mech. Stim.	% Change	Control	SO_2+ NaCl	% Change	Control	Mech. Stim.	% Change
	16.9	122	601	15.9	14.0	-11.9	16,8	80.1	389.9	15.9	19.1	20.1	17.9	82	338.5
	17.9			15.9	15.6	-1.9	15.9			15.9	17.9	12.6	19.5		
				15.9	14.2	-10.7				15.9	20.8	30.8			
Mean±	17.4	122		15.9	14.6		16.4	80.1		15.9	19.3		18.7	82	
S.D.	0.7			0	0.9		0.6			0	1.5		1.1		
	REFLEX INTACT			N.S.			REFLEX INTACT			Δ N.S.			REFLEX INTACT		
	Lung Compliance (c)														
	Control	Mech. Stim.	% Change	Control	Low SO_2	% Change	Control	Mech. Stim.	% Change	Control	SO_2+ NaCl	% Change	Control	Mech. Stim.	% Change
	8.0	3.6	-54.1	7.7	7.5	-2.6	8.1	8.1	3.8	7.7	7.0	-7.5	7.7	4.2	-44.0
	7.7			7.7	7.5	-2.6	7.5			7.5	7.1	-6.2	7.3		
				7.7	7.7	0				7.5	7.3	-3.5			
Mean±	7.9	3.6		7.7	7.6		7.8	8.1		7.6	7.1		7.5	4.2	
S.D.	0.2			0	0.1		0.4			0.1	0.2		0.3		
				N.S.						$P < 0.05$					
Sequence of Challenge (a)	(1)			(2)			(3)			(4)			(5)		

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm H_2O/1/sec.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

TABLE 8 (Continued)

Cat No. 1633

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

	Pulmonary Flow Resistance (b)												
	Control	NaCl	% Change	Control	Mech. Stim.	% Change	Control	High SO_2	% Change	Control	Mech. Stim.	% Change	
	15.9	19.1	20.1	17.9	112.5	565.7	15.9	16.9	6.3	17.9	100.3	409.1	
	15.9	21.5	35.2	15.9			15.9	14.0	-11.9	21.5			
		17.4	9.4					15.9	0				
Mean±	15.9	19.3		16.9	112.5		15.9	15.6		19.7	100.3		
S.D.	0	2.1		1.4			0	1.5		2.5			
		N.S.			REFLEX INTACT			Δ N.S.			REFLEX INTACT		
	Lung Compliance (c)												
	Control	NaCl	% Change	Control	Mech. Stim.	% Change	Control	High SO_2	% Change	Control	Mech. Stim.	% Change	
	8.1	6.9	-12.7	7.3	3.3	-54.2	7.1	8.6	22	7.7	5.4	2.3	
	7.7	6.9	-12.7	7.1			7.0	7.7	9.2	7.4			
		6.9	-12.7					7.4	5				
Mean±	7.9	6.9		7.2	3.3		7.0	7.9		7.6	5.4		
S.D.	0.3	0		0.1			0.1	0.6		0.2			
		N.S.						Δ N.S.					
Sequence of Challenge (a)		(6)			(7)			(8)			(9)		

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm H_2O/l/sec.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

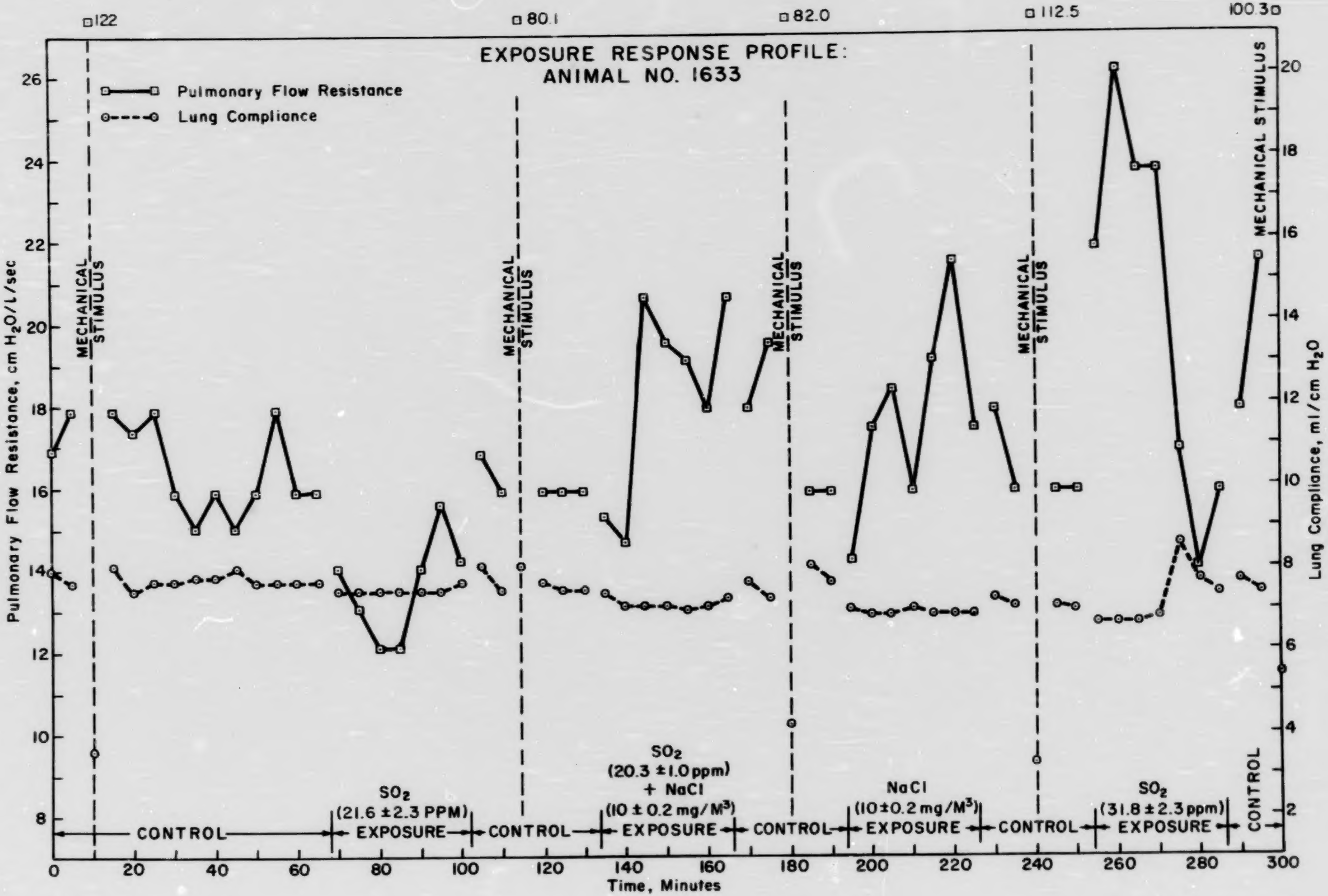

EXPOSURE RESPONSE PROFILE:
ANIMAL NO. 1633

TABLE 9

Cat No. 1606

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

	Control	Mech. Stim.	% Change	Control	Low SO_2	% Change	Control	Mech. Stim.	% Change	Control	SO_2+ NaCl	% Change	Control	Mech. Stim.	% Change
Pulmonary Flow Resistance (b)															
	19.9	127	538	19.9	15.7	-17.2	18.5	87.4	372.4	17.1	16.6	0.2	14.1	112	694.3
	19.9			18.5	15.7	-17.2				14.1	16.6	0.2			
				18.5	21.9	15.5				18.5	16.6	0.2			
Mean±	19.9	127		19.0	17.8		18.5	87.4		16.6	16.6		14.1	112	
S.D.	0			0.8	3.6					2.2	0				
	REFLEX INTACT			Δ N.S.			REFLEX INTACT			Δ N.S.			REFLEX INTACT		
Lung Compliance (c)															
	Control	Mech. Stim.	% Change	Control	Low SO_2	% Change	Control	Mech. Stim.	% Change	Control	SO_2+ NaCl	% Change	Control	Mech. Stim.	% Change
	9.7	6.9	-27.4	9.1	9.1	-7.2	9.7	4.7	-51.5	9.9	7.6	-20.8	8.4	4.1	-51.2
	9.3			9.3	9.3	0.0				10.2	7.3	-24			
				9.5	9.5	2.2				8.7	7.5	-21.9			
Mean±	9.5	6.9		9.3	9.3		9.7	4.7		9.6	7.5		8.4	4.1	
S.D.	0.3			0.2	0.2					0.8	0.2				
				Δ N.S.						P <0.05					
Sequence of Challenge (a)	(1)			(2)			(3)			(4)			(5)		

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm H_2O/1/sec.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

TABLE 9 (Continued)

Cat No. 1606

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

	Control	NaCl	% Change	Control	Mech. Stim.	% Change	Control	High SO_2	% Change	Control	Mech. Stim.	% Change	
Pulmonary Flow Resistance (b)													
	14.1	11.7	-31.3	19.2	96.3	401.6	19.9	22.3	17.6	18.5	61.1	230.3	
	18.5	11.6	-31.9				18.5	25.3	23.4				
	18.5	8.4	-50.7				18.5	19.9	4.9				
Mean±	17.0	10.6		19.2	96.3		19.0	22.5		18.5	61.1		
S.D.	2.5	1.9					0.8	2.7					
	P<0.05			REFLEX INTACT			Δ N.S.			REFLEX INTACT			
Lung Compliance (c)													
	9.3	7.6	-14.6	8.5	4.1	-51.8	6.7	8.2	16.6	7.9	8.5	7.6	
	8.9	7.6	-14.6				7.2	7.2	2.4				
	8.5	7.7	-13.5				7.2	7.1	0.9				
Mean±	8.9	7.6		8.5	4.1		7.0	7.5		7.9	8.5		
S.D.	0.4	0.1					0.3	0.6					
	P<0.05						ΔN.S.						
Sequence of Challenge(a)	(6)			(7)			(8)			(9)			

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm H_2O/1/sec.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

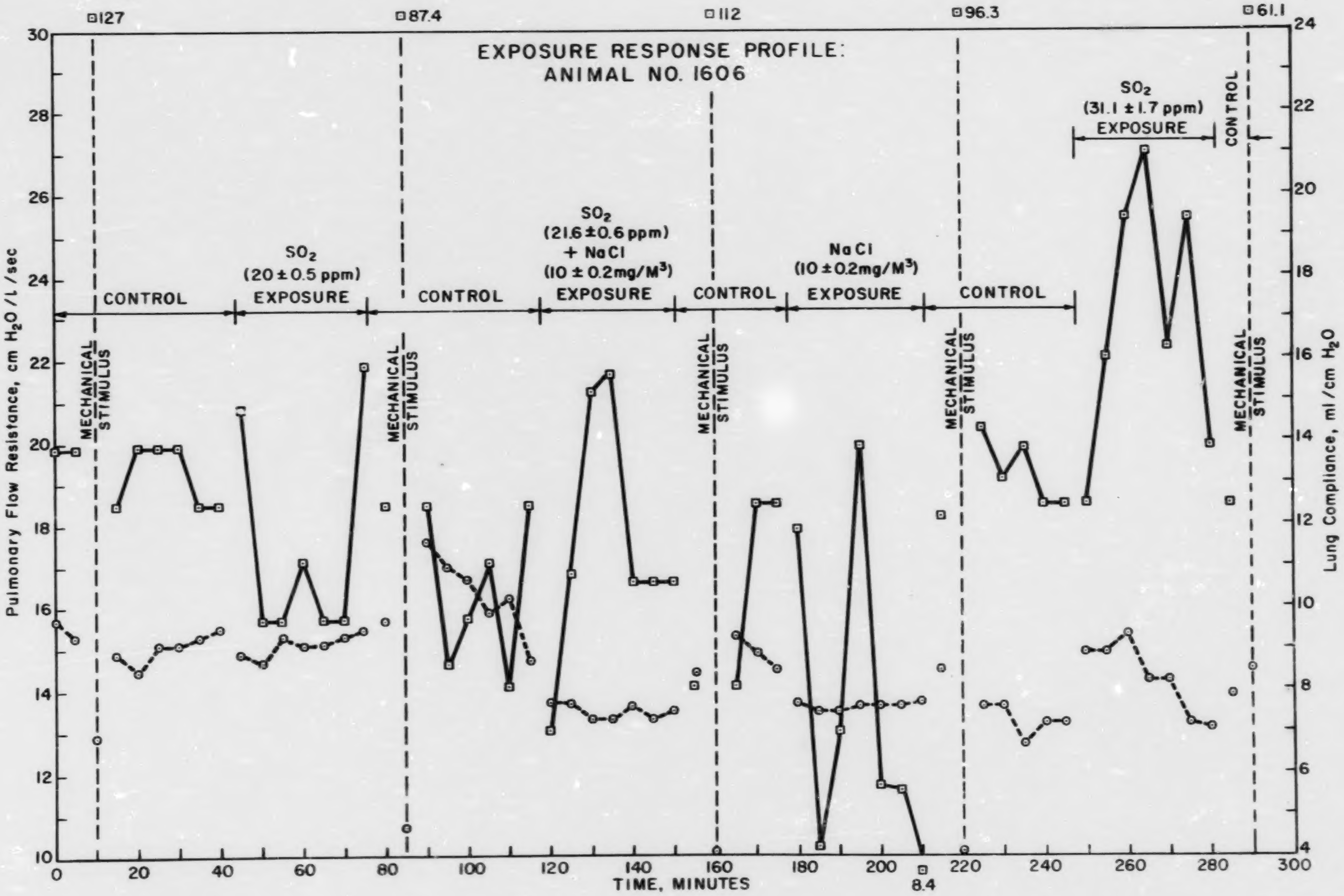

EXPOSURE RESPONSE PROFILE:
ANIMAL NO. 1606
Pulmonary Flow Resistance, cm H_2O/l/sec
Lung Compliance, ml/cm H_2O
TIME, MINUTES
0
20
40
60
80
100
120
140
160
180
200
220
240
260
280
300
10
12
14
16
18
20
22
24
26
28
30
4
6
8
10
12
14
16
18
20
22
24
127
87.4
112
96.3
61.1
8.4
MECHANICAL STIMULUS
CONTROL
SO_2 (20 ± 0.5 ppm) EXPOSURE
MECHANICAL STIMULUS
CONTROL
SO_2 (21.6 ± 0.6 ppm) + NaCl (10 ± 0.2mg/M^3) EXPOSURE
MECHANICAL STIMULUS
CONTROL
NaCl (10 ± 0.2mg/M^3) EXPOSURE
MECHANICAL STIMULUS
CONTROL
SO_2 (31.1 ± 1.7 ppm) EXPOSURE
CONTROL
MECHANICAL STIMULUS

TABLE 10

Cat No. 1112

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

Pulmonary Flow Resistance (b)

	Control	Low SO_2	% Change	Control	Mech. Stim.	% Change	Control	SO_2+ NaCl	% Change	Control	Mech. Stim.	% Change	Control	NaCl	% Change
	18.1	27.6	57.1	19.7	65.7	233.5	18.1	25.9	43.1	18.9	49.8	156.2	18.9	14.9	-23.3
	18.1	29.2	66.2	19.7			18.1	34.4	90.1	19.7			19.7	20.3	4.5
	16.5	27.6	57.1	19.7			18.1	28.8	59.1	19.7			19.7	23.1	18.9
Mean±	17.6	28.1		19.7	65.7		18.1	29.7		19.4	49.8		19.4	19.4	
S.D.	0.9	0.9		0			0	4.3		0.5			0.5	4.2	
t-test		P< 0.01			REFLEX INTACT			p< 0.05			REFLEX INTACT			Δ N.S.	

Lung Compliance (c)

	Control	Low SO_2	% Change	Control	Mech. Stim.	% Change	Control	SO_2+ NaCl	% Change	Control	Stim.	% Change	Control	NaCl	% Change
	15.5	12.8	-4.2	11.5	11.5	+0.0	11.3	12.8	13.6	11.5	16.0	47.7	11.5	9.2	-15.1
	12.8	13.2	-1.2	11.3			11.0	14.5	28.7	10.5			10.5	10.0	-7.7
	11.8	12.8	-4.2	11.8			11.5	12.5	10.9	10.5			10.5	9.2	-15.1
Mean±	13.4	12.9		11.5	11.5		11.3	13.3		10.8	16.0		10.8	9.5	
S.D.	1.9	0.2		0.3			0.3	1.1		0.6			0.6	0.5	
t-test		Δ N.S.						Δ N.S.						-0.05	
Sequence of Challenge (a)		(1)			(2)			(3)			(4)			(5)	

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm $H_2O/1/sec$.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant (P>0.05)

TABLE 10 (Continued)

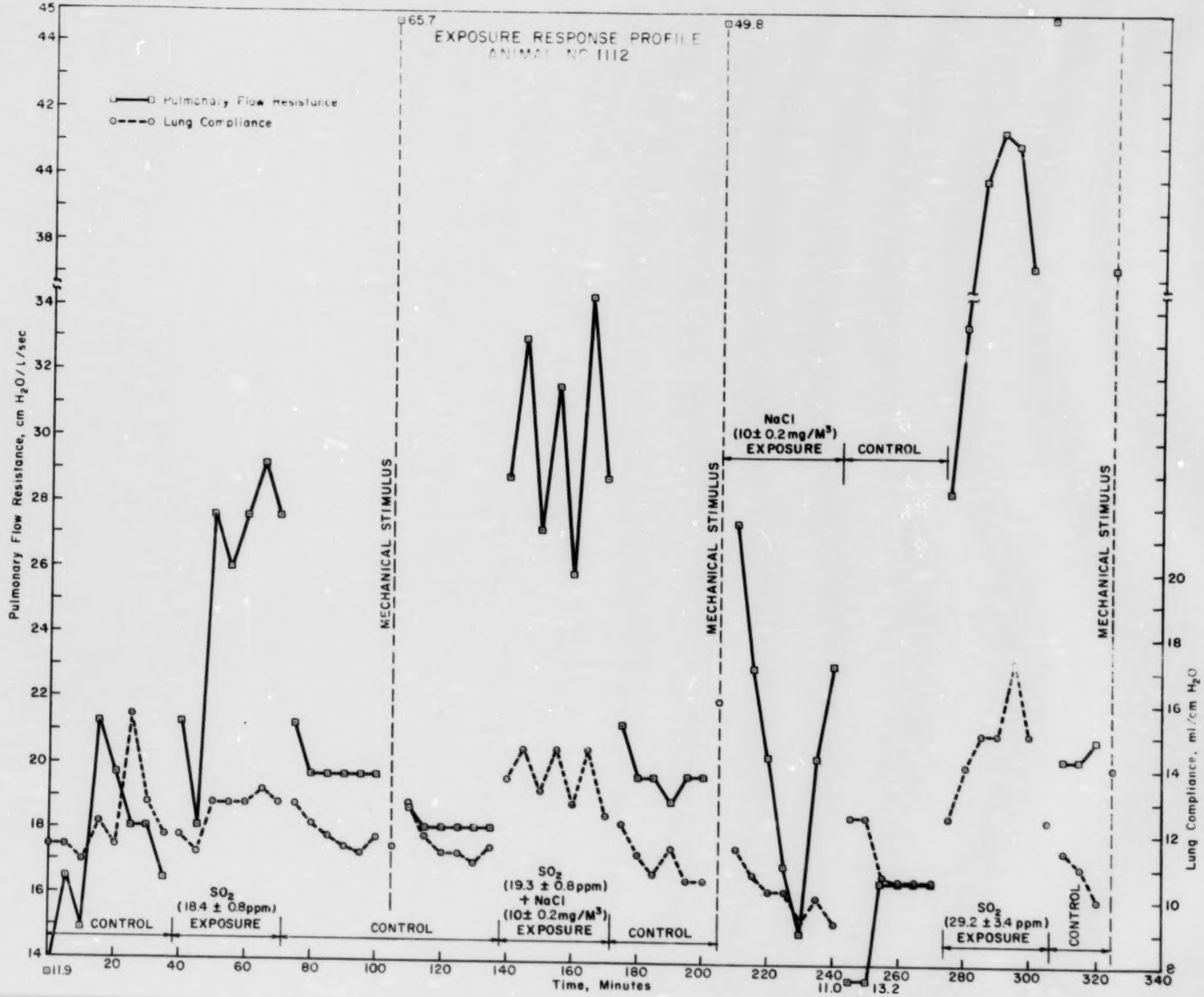
Cat No. 1112

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

Pulmonary Flow Resistance (b)									
	Control	High SO_2	% Change	Control	Mech. Stim.	% Change			
	16.5	41.1	149.1	20.3	37.3	82			
	16.5	37.3	126.1	20.3					
	16.5	44.9	172.1	20.9					
Mean±	16.5	41.1		20.5	37.3				
S.D.	0	3.8		0.3					
t-test		P<0.01							
				REFLEX INTACT					
Lung Compliance (c)									
	Control	High SO_2	% Change	Control	Stim.	% Change			
	10.5	17.2	63.8	11.5	14.0	29.6			
	10.5	15.0	42.9	11.0					
	10.5	18.6	77.1	10.0					
Mean±	10.5	16.9		10.8	14.0				
S.D.	0	1.8		0.8					
t-test		P< 0.05							
Sequence of Challenge (a)		(6)			(7)				

*Control for 15 minutes preceding challenge.
(a) See Figure.
(b) Pulmonary Flow Resistance, Cm H_2O/1/sec.
(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)



EXPOSURE RESPONSE PROFILE
ANIMAL NO 1112

TABLE 11

Cat No. 1609

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

	Control	Mech. Stim.	% Change	Control	Low SO_2	% Change	Control	Mech. Stim.	% Change	Control	SO_2+ NaCl	% Change	Control	Mech. Stim.	% Change
Pulmonary Flow Resistance (b)															
	19.3	114	483.6	20.1	19.3	6.6	18.1	162	795	18.1	18.1	0	15.8	72.5	398.3
	20.5			18.1	20.5	13.3				18.1	20.5	13.3	13.3		
	18.8			18.1	20.5	13.3				17.0	15.8	-12.7			
Mean±	19.5	114		19.0	20.1		18.1	162		17.7	18.1		14.6	72.5	
S.D.	0.9			1.0	0.7					0.6	2.4		1.8		
	REFLEX INTACT			Δ N.S.			REFLEX INTACT			Δ N.S.			REFLEX INTACT		
Lung Compliance (c)															
	Control	Mech. Stim.	% Change	Control	Low SO_2	% Change	Control	Mech. Stim.	% Change	Control	SO_2+ NaCl	% Change	Control	Mech. Stim.	% Change
	8.9	5.0	-44.9	9.4	8.5	-9.6	9.7	4.5	-53.6	9.7	9.4	-5.1	10.6	7.9	-24.4
	9.1			9.2	9.4	1.1				10.1	9.4	-5.1	10.3		
	9.2			9.2	8.9	-4.3				9.9	9.4	-5.1			
Mean±	9.1	5.0		9.3	8.9		9.7	4.5		9.9	9.4		10.5	7.9	
S.D.	0.2			0.1	0.5					0.2	0		0.2		
				Δ N.S.						Δ N.S.					
Sequence of Challenge (a)	(1)			(2)			(3)			(4)			(5)		

*Control for 15 minutes preceding challenge.
(a) See Figure.
(b) Pulmonary Flow Resistance, Cm H_2O/1/sec.
(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

TABLE 11 (Continued)

Cat No. 1609

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

Pulmonary Flow Resistance (b)									
	Control	High SO_2	% Change	Control	Mech. Stim.	% Change			
	17.0	17.6	-2.8	15.8	122.7	676.6			
	19.1	22.8	26.0						
	18.1	21.7	19.9						
Mean± S.D.	17.7 0.6	20.7 2.7		15.8	122.7				
t-test		Δ N.S.			REFLEX INTACT				
Lung Compliance (c)									
	Control	High SO_2	% Change	Control	Mech. Stim.	% Change			
	9.9	9.2	-7.7	9.9	5.3	-46.5			
	9.9	9.4	-5.7						
	10.1	8.2	-7.7						
Mean± S.D.	10.0 0.1	8.9 0.6		9.9	5.3				
t-test		Δ N.S.							
Sequence of Challenge (a)		(6)			(7)				

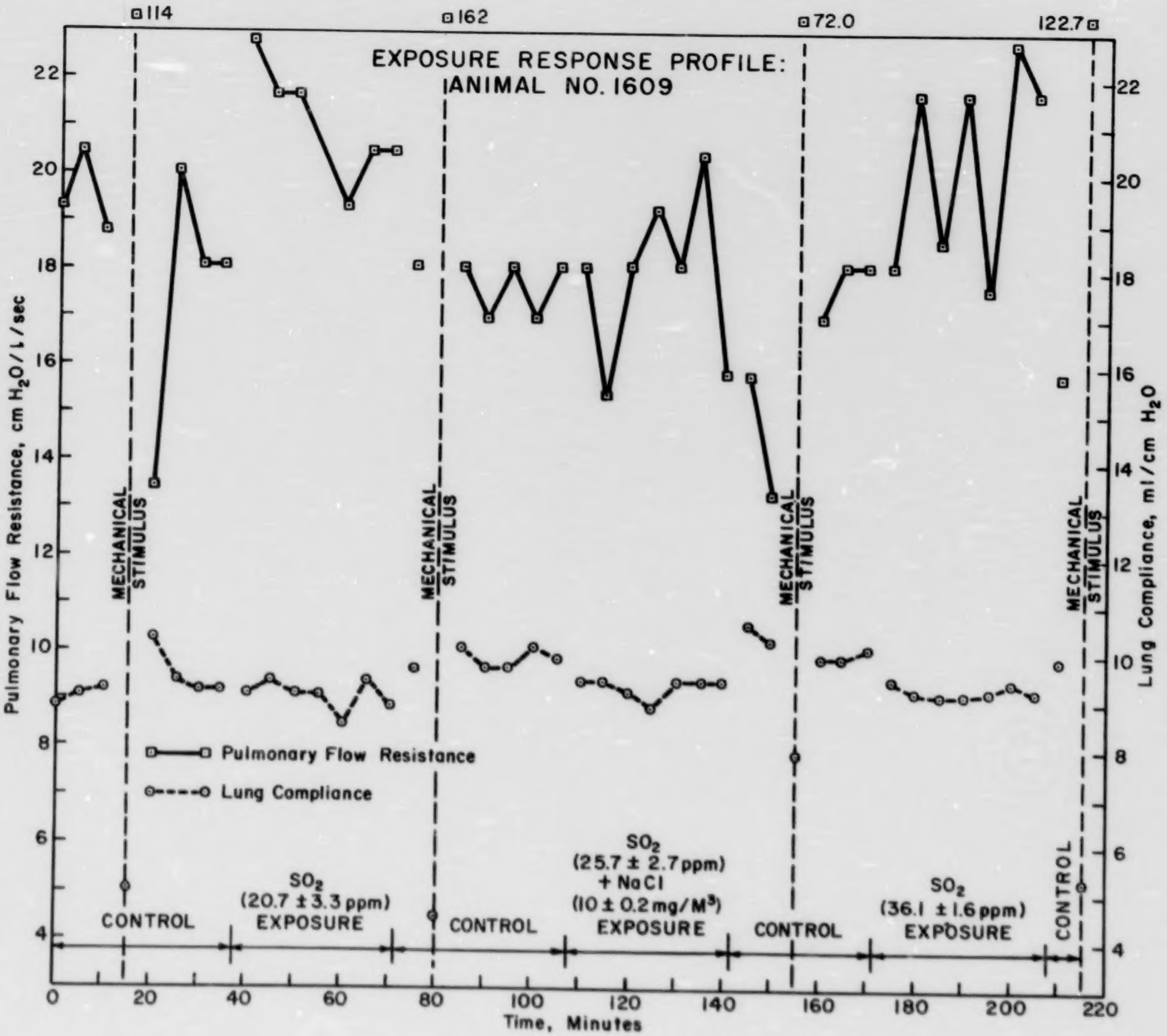
*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm $H_2O/1/sec$.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)



EXPOSURE RESPONSE PROFILE: ANIMAL NO. 1609

TABLE 12

Cat No. 1564

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

Pulmonary Flow Resistance (b)															
	Control	Mech. Stim.	% Change	Control	Low SO_2	% Change	Control	Mech. Stim.	% Change	Control	SO_2+ NaCl	% Change	Control	Mech. Stim.	% Change
	11.1	76.8	645.6	9.7	7.1	-29.9	8.4	121.7	1337.4	11.0	9.5	8.8	11.0	29.5	237.8
	9.9			9.7	8.4	-17.1	7.1			7.6	8.8	0.8	7.6		
	9.9			11.0	9.5	-6.2	9.9			7.6	8.8	0.8	7.6		
Mean±	10.3	76.8		10.1	8.3		8.5	121.7		8.7	9.0		8.7	29.5	
S.D.	0.7			0.8	1.2		1.4			2.0	0.4		2.0		
	REFLEX INTACT			Δ N.S.			REFLEX INTACT			Δ N.S.			REFLEX INTACT		

Lung Compliance (c)															
	Control	Mech. Stim.	% Change	Control	Low SO_2	% Change	Control	Mech. Stim.	% Change	Control	SO_2+ NaCl	% Change	Control	Mech. Stim.	% Change
	9.9	6.3	-36.4	14.6	14.2	1.2	20.1	9.9	-49.5	11.2	12.9	19.1	11.2	8.1	-25.2
	9.9			14.2	12.9	-8.1	17.6			11.2	12.2	12.2	11.2		
	9.9			13.3	13.2	-5.2	21.1			10.1	23.4	116.0	10.1		
Mean±	9.9	6.3		14.0	13.4		19.6	9.9		10.8	16.2		10.8		
S.D.	0			0.7	0.7		1.8			0.6	6.3		0.6		
				Δ N.S.						Δ N.S.					
Sequence of Challenge(a)	(1)			(2)			(3)			(4)			(5)		

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm $H_2O/1/sec$.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

TABLE 12 (Continued)

Cat No. 1564

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

Pulmonary Flow Resistance (b)							
	Control	High SO_2	% Change				
	9.7	7.1	-23.4				
	8.4	5.2	-43.9				
	9.7	5.9	-37.4				
Mean±	9.3	6.0					
S.D.	0.9	1.0					
		$P < 0.01$					
Lung Compliance (c)							
	Control	High SO_2	% Change				
	19.2	16.3	7.9				
	10.9	13.7	-9.3				
	15.2	14.6	-3.3				
Mean±	15.1	14.9					
S.D.	4.2	1.3					
		Δ N.S.					
Sequence of Challenge (a)	(6)						

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm H_2O/1/sec.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

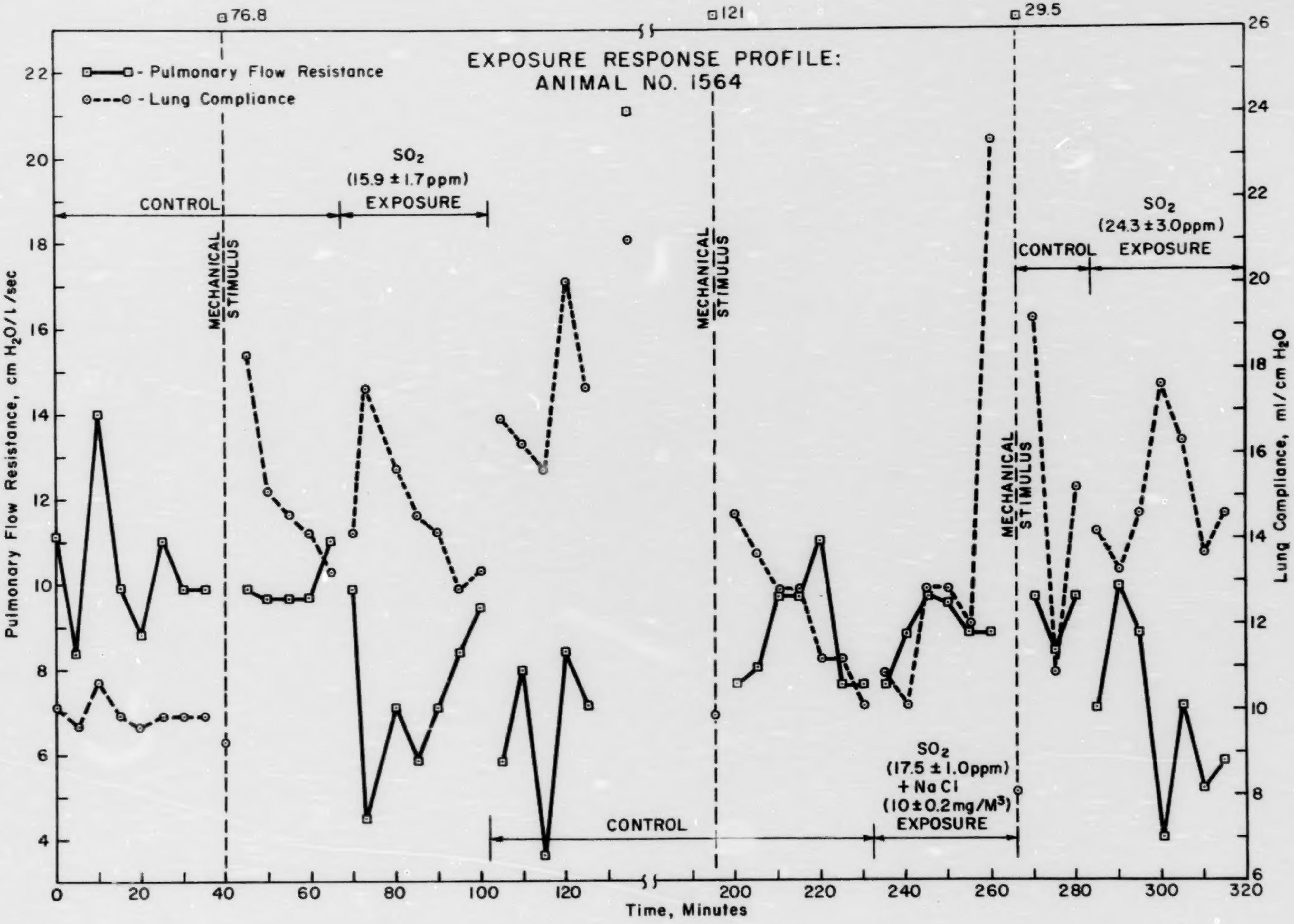

EXPOSURE RESPONSE PROFILE:
ANIMAL NO. 1564
- Pulmonary Flow Resistance
- Lung Compliance
Pulmonary Flow Resistance, cm H_2O/l/sec
Lung Compliance, ml/cm H_2O
Time, Minutes
76.8
121
29.5
CONTROL
MECHANICAL STIMULUS
SO_2
(15.9 ± 1.7ppm)
EXPOSURE
CONTROL
MECHANICAL STIMULUS
SO_2
(17.5 ± 1.0ppm)
+ NaCl
(10 ± 0.2mg/M³)
EXPOSURE
MECHANICAL STIMULUS
CONTROL
SO_2
(24.3 ± 3.0ppm)
EXPOSURE
0
20
40
60
80
100
120
200
220
240
260
280
300
320
4
6
8
10
12
14
16
18
20
22
6
8
10
12
14
16
18
20
22
24
26

TABLE 13

Cat No. 1593

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

	Control	Mech. Stim.	% Change	Control	Low SO_2	% Change	Control	Mech. Stim.	% Change	Control	SO_2+ NaCl	% Change	Control	Mech. Stim.	% Change
Pulmonary Flow Resistance (b)															
	8.2	110	1298	11.1	6.4	-33.1	11.1	80.1	731.5	9.0	10.1	3.8	10.1	82.8	719.8
	9.0			8.8	11.2	17.1	9.0			10.1	12.4	27.4			
	6.4			8.8	5.8	-39.4	9.8			10.1	8.8	-9.6			
Mean$\pm$	7.9	110		9.6	7.8		9.6	80.1		9.7	10.4		10.1	82.8	
S.D.	1.3			1.3	3.0		1.3			0.6	1.8				
t-test	REFLEX INTACT			Δ N.S.			REFLEX INTACT			Δ N.S.			REFLEX INTACT		
Lung Compliance (c)															
	Control	Mech. Stim.	% Change	Control	Low SO_2	% Change	Control	Mech. Stim.	% Change	Control	SO_2+ NaCl	% Change	Control	Mech. Stim.	% Change
	10.4	6.0	-55.4	15.2	17.3	11.4	17.3	4.9	-73.8	14.7	18	22.2	20.2	6.4	-68.3
	10.4			15.2	16.7	7.5	19.4			15.2	15.2	3.2			
	19.4			16.2	17.3	11.4	19.4			14.3	15.7	6.6			
Mean$\pm$	13.5	6.0		15.5	17.1		18.7	4.9		14.7	16.3		20.2	6.4	
S.D.	5.3			0.6	0.3		1.2			0.5	1.5				
t-test				$p < 0.05$						Δ N.S.					
Sequence of Challenge (a)	(1)			(2)			(3)			(4)			(5)		

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm H_2O/1/sec.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

TABLE 13 (Continued)

Cat No. 1593

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

	Control	High SO_2	% Change	Control	Mech. Stim.	% Change			
Pulmonary Flow Resistance [b]									
	11.1	13.5	19.8	11.1	67.4	464.9			
	8.9	14.3	23.2	8.8					
	15.9	14.7	13.1	15.9					
Mean ±	11.9	14.2		11.9	67.4				
S.D.	3.6	0.6		3.6					
t-test	Δ N.S.			REFLEX INTACT					
Lung Compliance [c]									
	18	15.2	-14.4	18	4.6	-74.1			
	18	15.2	-14.4	18					
	17.3	15.2	-17.3	17.3					
Mean ±	17.8	15.2		17.8	4.6				
S.D.	0.4	0		0.4					
t-test	P< 0.01								
Sequence of Challenge [(a)]	(6)			(7)					

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm H_2O/1/sec.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

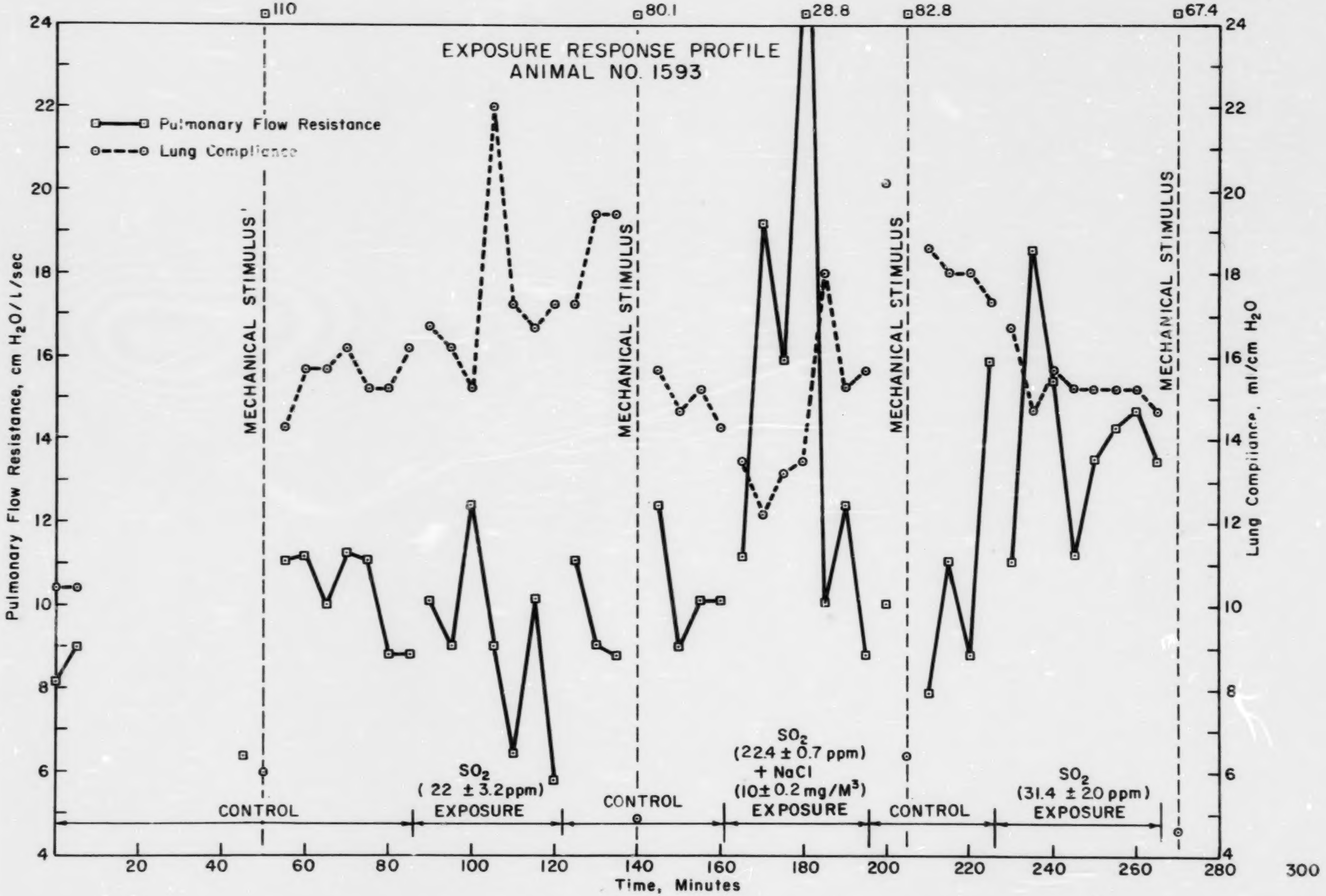

EXPOSURE RESPONSE PROFILE
ANIMAL NO. 1593
Pulmonary Flow Resistance
Lung Compliance
Pulmonary Flow Resistance, cm H_2O/l/sec
Lung Compliance, ml/cm H_2O
Time, Minutes
110
80.1
28.8
82.8
67.4
MECHANICAL STIMULUS'
MECHANICAL STIMULUS
MECHANICAL STIMULUS
MECHANICAL STIMULUS
CONTROL
SO_2
(22 ± 3.2 ppm)
EXPOSURE
CONTROL
SO_2
(22.4 ± 0.7 ppm)
+ NaCl
(10 ± 0.2 mg/M³)
EXPOSURE
CONTROL
SO_2
(31.4 ± 2.0 ppm)
EXPOSURE
4
6
8
10
12
14
16
18
20
22
24
20
40
60
80
100
120
140
160
180
200
220
240
260
280
300

TABLE 14 (Continued)

Cat No. 1566

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

	Control	Mech. Stim.	% Change	Control	Mech. Stim.	% Change	Control	High SO_2	% Change	Control	
Pulmonary Flow Resistance (b)											
	9.6	175.1	1724	10.7	201	1613	15.0	18.5	32.1	14.8	
	9.6			9.2			13.5	11.3	-19.3	16.9	
	9.6			15.3			13.5	12.2	-12.9		
Mean±	9.6	175.1		11.7	201		14.0	14.0		15.9	
S.D.	0			3.2			0.9	3.8		1.5	
t-test	REFLEX INTACT			REFLEX INTACT			Δ N.S.				
Lung Compliance (c)											
	7.5	4.5	-35.7	8.5	4.5	-46.2	8.1	7.9	0.9	8.1	
	6.7			5.5			7.9	7.5	-4.3	7.7	
	6.8			11.1			7.5	7.5	-4.3		
Mean±	7.0	4.5		8.4	4.5		7.8	7.6		7.9	
S.D.	0.4			2.8			0.3	0.2		0.3	
t-test							Δ N.S.				
Sequence of Challenge (a)	(6)			(7)			(8)			(9)	

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm $H_2O/1/sec$.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

TABLE 14

Cat No. 1566

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

	Pulmonary Flow Resistance (b)														
	Control	Mech. Stim.	% Change	Control	Mech. Stim.	% Change	Control	Low SO_2	% Change	Control	Mech. Stim.	% Change	Control	SO_2+ NaCl	% Change
	11.9	93.5	646	8.8	232.2	2318.8	9.2	10.0	8.7	11.9	112.2	984.1	9.6	13.5	40.6
	13.6			10.4			9.2	10.2	10.9	8.8			9.6	11.1	15.6
	12.1						9.2	10.4	13.0				9.6	15.0	56.3
Mean±	12.5	93.5		9.6	232.2		9.2	10,2		10.4	112.2		9.6	13.2	
S.D.	0.9			1.1			0	0.2		2.2			0	2.0	
t-test	REFLEX INTACT			REFLEX INTACT			P<0.05			REFLEX INTACT			Δ N.S.		
	Lung Compliance (c)														
	Control	Mech. Stim.	% Change	Control	Mech. Stim.	% Change	Control	Low SO_2	% Change	Control	Mech. Stim.	% Change	Control	SO_2+ NaCl	% Change
	5.9	6.6	11.9	9.1	3.3	-62.1	9.4	6.9	-23.9	7.2	4.1	-43.8	7.5	5.7	-18.6
	5.9			8.3			8.9	6.8	-25	7.4			6.7	6.8	-2.9
	5.9						8.9	6.8	-25				6.8	5.8	-17.1
Mean±	5.9	6.6		8.7	3.3		9.1	6.8		7.3	4.1		7.0	6.1	
	0			0.6			0.3	0.1		0.1			0.4	0.6	
t-test							P<0.01						Δ N.S.		
Sequence of Challenge (a)	(1)			(2)			(3)			(4)			(5)		

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm H_2O/1/sec.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

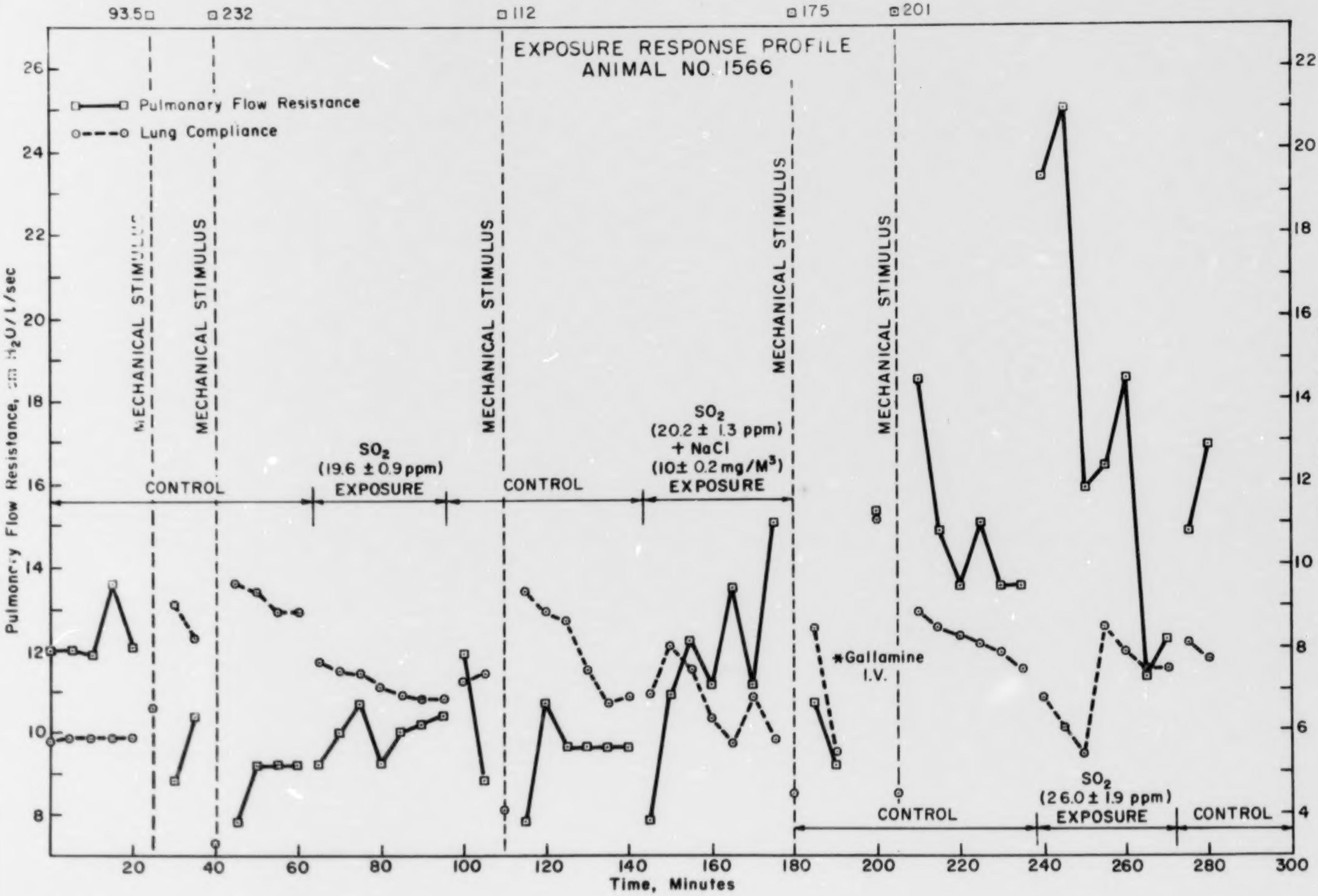

EXPOSURE RESPONSE PROFILE
ANIMAL NO. 1566
Pulmonary Flow Resistance
Lung Compliance
93.5
232
112
175
201
MECHANICAL STIMULUS
MECHANICAL STIMULUS
MECHANICAL STIMULUS
MECHANICAL STIMULUS
MECHANICAL STIMULUS
CONTROL
SO_2
(19.6 ± 0.9 ppm)
EXPOSURE
CONTROL
SO_2
(20.2 ± 1.3 ppm)
+ NaCl
(10 ± 0.2 mg/M^3)
EXPOSURE
*Gallamine
I.V.
CONTROL
SO_2
(26.0 ± 1.9 ppm)
EXPOSURE
CONTROL
Pulmonary Flow Resistance, cm H_2O/l/sec
8
10
12
14
16
18
20
22
24
26
Lung Compliance, ml/cm H_2O
4
6
8
10
12
14
16
18
20
22
Time, Minutes
20
40
60
80
100
120
140
160
180
200
220
240
260
280
300

TABLE 15

Cat No. 1113

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

	Control	Mech. Stim.	% Change	Control	Low SO_2	% Change	Control	Mech. Stim.	% Change	Control	SO_2+ NaCl	% Change	Control	High SO_2	% Change
Pulmonary Flow Resistance [(b)]															
	16.1	233.2	1348	16.1	19.2	19.3	15.2	129.3	718	16.1	10.8	-32.9	16.1	21.2	31.7
	16.1			16.1	17.8	10.6	16.1			16.1	18.8	16.8	16.1	19.5	31.1
	16.1			16.1	24.6	52.8	16.1				8.8	-45.3	16.1	17.8	10.6
Mean±	16.1	233.2		16.1	20.5		15.8	129.3		16.1	12.8		16.1	19.5	
S.D.	0			0	3.6		0.5			0	5.3		0	1.7	
	REFLEX INTACT			Δ N.S.			REFLEX INTACT			Δ N.S.			Δ N.S.		
Lung Compliance [(c)]															
	12.4	4.7	-60.3	11.1	12.0	6.2	11.4	5.0	-55.5	10.9	9.1	-20.2	11.1	10.8	-0.9
	12			11.1	11.4	0.9	11.1			12.0	10.2	-10.5	11.1	10.8	-0.9
	11.1			11.7	12.4	9.7	11.1				9.1	-20.2	10.5	10.5	-3.7
Mean±	11.8	4.7		11.3	11.9		11.2	5.0		11.4	9.5		10.9	10.7	
S.D.	0.7			0.3	0.5		0.2			0.8	0.6		0.3	0.2	
				Δ N.S.						Δ N.S.			Δ N.S.		
Sequence of Challenge [(a)]	(1)			(2)			(3)			(4)			(5)		

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm H_2O/l/sec.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

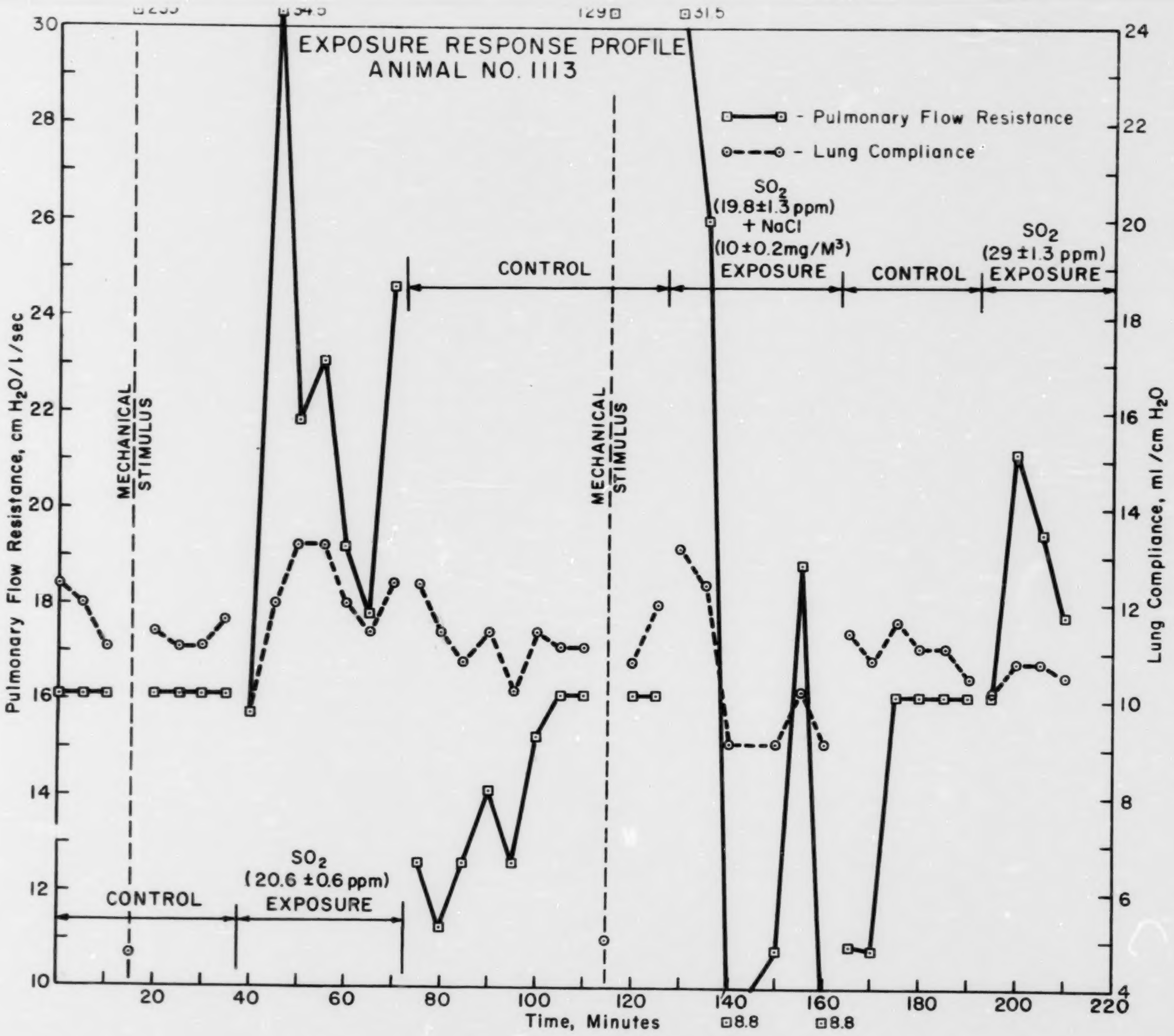

□235
□34.5
129□
□31.5
EXPOSURE RESPONSE PROFILE
ANIMAL NO. 1113
□—□ - Pulmonary Flow Resistance
⊙- - -⊙ - Lung Compliance
MECHANICAL STIMULUS
MECHANICAL STIMULUS
CONTROL
SO_2 (20.6 ±0.6 ppm) EXPOSURE
CONTROL
SO_2 (19.8±1.3 ppm) + NaCl (10±0.2mg/M³) EXPOSURE
CONTROL
SO_2 (29 ±1.3 ppm) EXPOSURE
Pulmonary Flow Resistance, cm H_2O/1/sec
10
12
14
16
18
20
22
24
26
28
30
Lung Compliance, ml /cm H_2O
4
6
8
10
12
14
16
18
20
22
24
Time, Minutes
20
40
60
80
100
120
140
160
180
200
220
□8.8
□8.8

TABLE 16

Cat No. 1482

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

	Pulmonary Flow Resistance [b]												
	Control	Mech. Stim.	% Change	Control	Low SO_2	% Change	Control	SO_2+ NaCl	% Change	Control	High SO_2	% Change	Control
	49.0	70	88.7	20.8	20.1	-11.1	24.6	22.1	7.1	20.5	11.8	-42.7	18.4
	35.9			23.9	21.6	-4.4	19.1	23.3	12.9	23.3	10	-51.5	11.7
	26.5			23.1	19.1	-15.5	18.2	26.7	29.4	18	13.9	-32.5	
Mean±	37.1	70		22.6	20.3		20.6	24.0		20.6	11.9		15.1
S.D.	11.3			1.6	1.3		3.5	2.4		2.7	2.0		4.7
	REFLEX INTACT				Δ N.S.			Δ N.S.			P < 0.01		
	Lung Compliance [c]												
	Control	Mech. Stim.	% Change	Control	Low SO_2	% Change	Control	SO_2+ NaCl	% Change	Control	High SO_2	% Change	Control
	9.4	17.6	74.3	9.9	10.1	0.7	14.1	14.6	11.5	13.3	10.4	-11.6	8.4
	9.3			9.3	11.8	17.6	11.5	14.6	11.5	10.5	8.4	-28.6	10.1
	12.5			10.9	11.2	11.6	13.7	12.9	-1.5	11.5	8.4	-28.6	
Mean±	10.1	17.6		10.0	11.0		13.1	14.0		11.8	9.1		9.3
S.D.	2.2			0.8	0.9		1.4	1.0		1.4	1.2		1.2
					Δ N.S.			Δ N.S.			P< 0.05		
Sequence of Challenge[a]		(1)			(2)			(3)			(4)		(5)

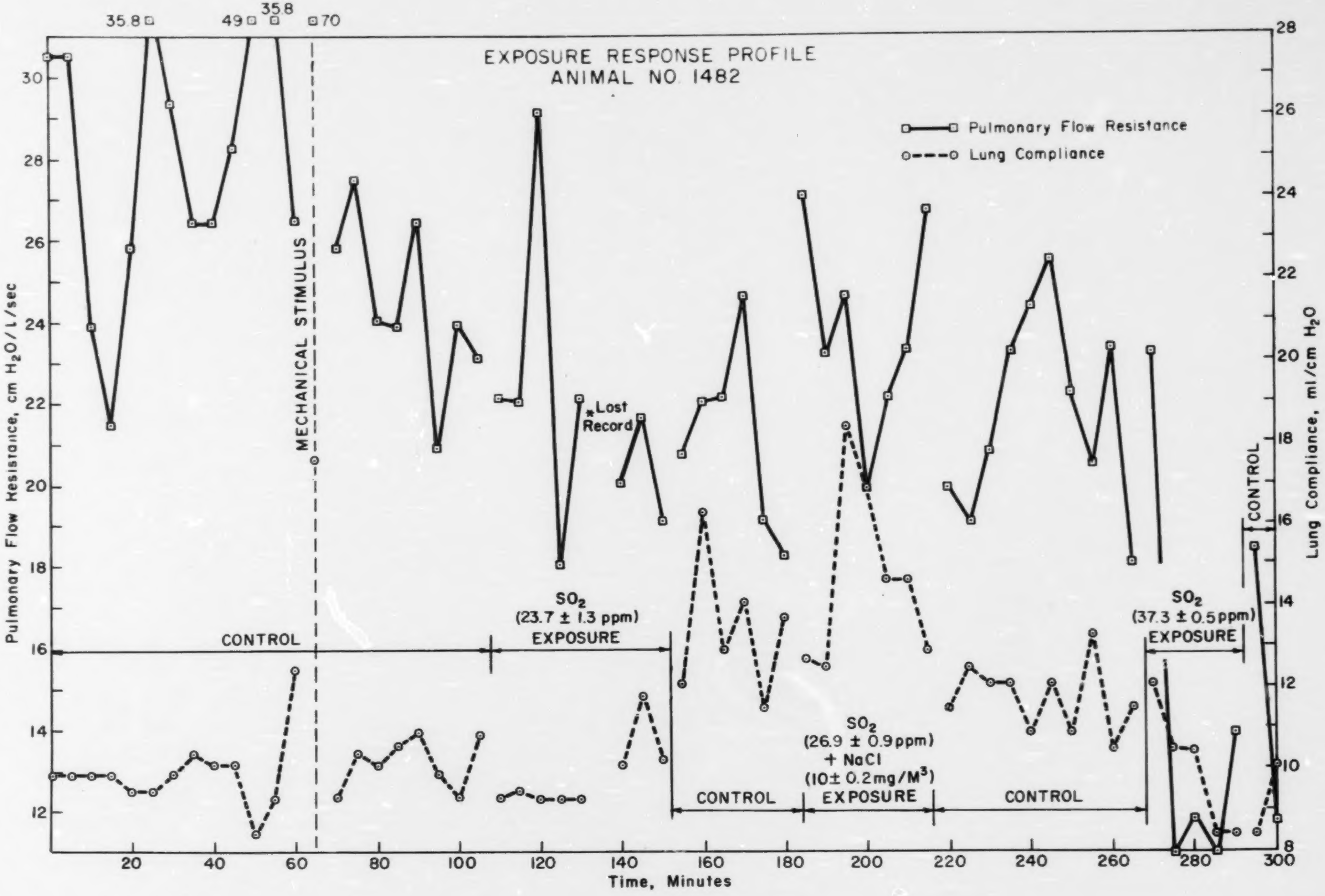
*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm H_2O/1/sec.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)



EXPOSURE RESPONSE PROFILE
ANIMAL NO. 1482

TABLE 17

Cat No. 1611

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

	Control	Mech. Stim.	% Change	Control	Low SO_2	% Change	Control	Mech. Stim.	% Change	Control	SO_2+ NaCl	% Change	Control	Mech. Stim.	% Change
Pulmonary Flow Resistance (b)															
	17.7	135.6	666.1	17.7	24.6	35.9	17.7	167.4	845.8	17.7	25.7	45.2	17.7	97.0	448
	17.7			18.9	21.2	17.1				17.7	22.2	25.4			
				17.7	22.3	23.2				17.7	22.3	26.0			
Mean±	17.7	135.6		18.1	22.7		17.7	167.4		17.7	23.4		17.7	97.0	
S.D.	0			0.7	1.7					0	2.0				
	REFLEX INTACT			$P<0.05$			REFLEX INTACT			$P< 0.05$			REFLEX INTACT		
Lung Compliance (c)															
	Control	Mech. Stim.	% Change	Control	Low SO_2	% Change	Control	Mech. Stim.	% Change	Control	SO_2+ NaCl	% Change	Control	Mech. Stim.	% Change
	9.5	4.5	-52.6	8.9	8.1	-8.6	9.1	4.8	-47.3	10.5	8.6	-11.9	9.8	4.6	-53.1
	9.5			8.8	8.6	-3.0				10.0	8.2	-16.0			
				8.9	8.4	-5.3				8.8	8.6	-11.9			
Mean±	9.5	4.5		8.7	8.4		9.1	4.8		9.8	8.5		9.8	4.6	
S.D.	0			0.1	0.3					0.9	0.2				
				Δ N.S.						Δ N.S.					
Sequence of Challenge (a)	(1)			(2)			(3)			(4)			(5)		

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm H_2O/1/sec.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

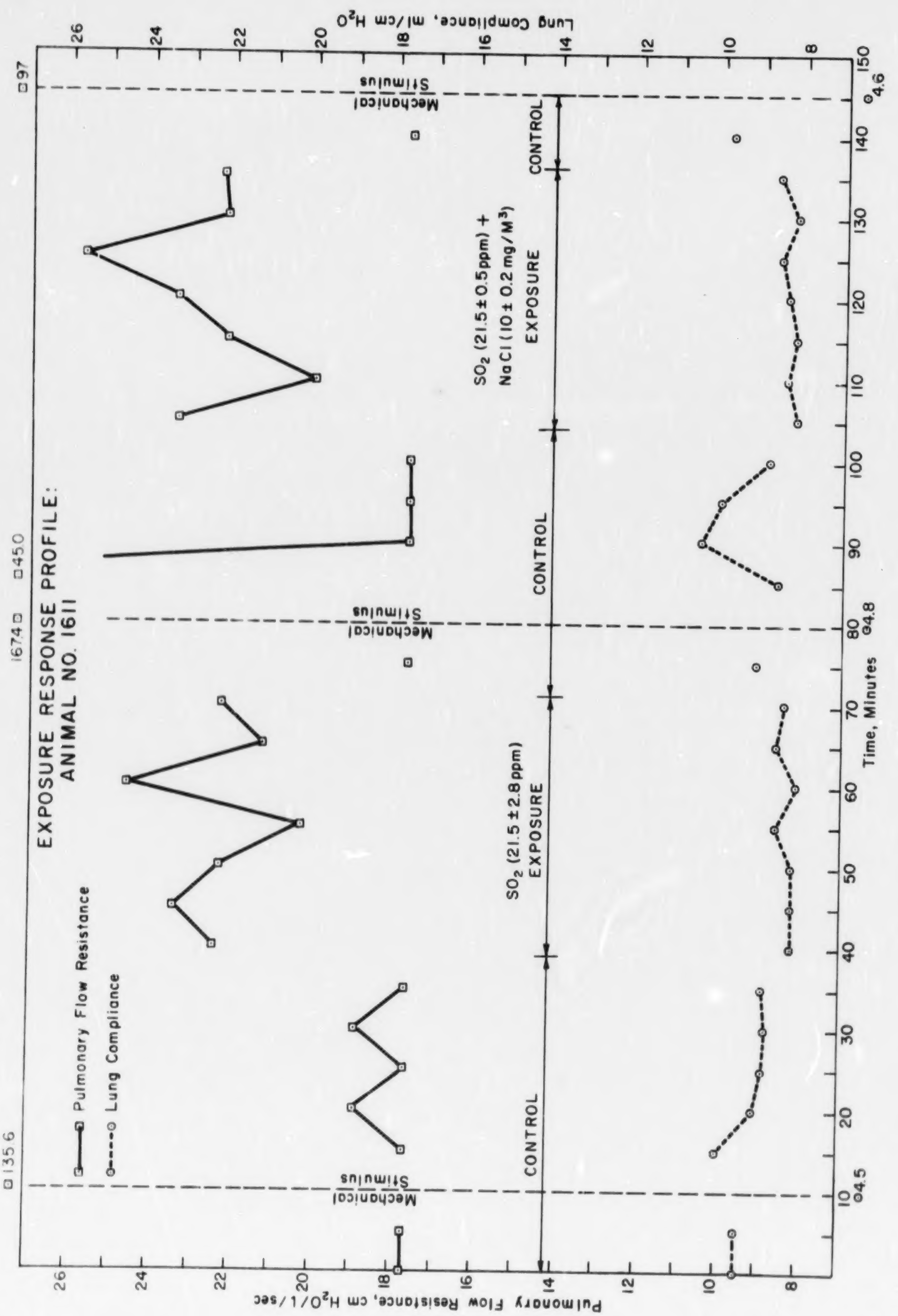

EXPOSURE RESPONSE PROFILE:
ANIMAL NO. 1611
Pulmonary Flow Resistance
Lung Compliance
Pulmonary Flow Resistance, cm H_2O/1/sec
Lung Compliance, ml/cm H_2O
Time, Minutes
Mechanical Stimulus
Mechanical Stimulus
Mechanical Stimulus
CONTROL
SO_2 (21.5 ± 2.8 ppm) EXPOSURE
CONTROL
SO_2 (21.5 ± 0.5 ppm) + NaCl (10 ± 0.2 mg/M^3) EXPOSURE
CONTROL
135.6
167.4
450
97
4.5
4.8
4.6
8
10
12
14
16
18
20
22
24
26
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150

TABLE 18

Cat No. 1478

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

	Control	Mech. Stim.	% Change	Control	Low SO_2	% Change	Control	Mech. Stim.	% Change	Control	SO_2+ NaCl	% Change	Control	Mech. Stim.	% Change
Pulmonary Flow Resistance [(b)]															
	22.4	115	413	17.5 16.9 18.7	21.2 17.3 21.2	19.8 -2.3 19.8	17.3	104		19 19 19	19 21.2 17.3	0 11.6 -8.9	17.7	89	403
Mean± S.D.	22.4	115		17.7	19.9		17.3	104		19.0 0	19.2 2.0		17.7	89	
t-test	REFLEX INTACT			Δ N.S.			REFLEX INTACT			Δ N.S.			REFLEX INTACT		
Lung Compliance [(c)]															
	22.6	33.5	49.2	22.6 22.6 22.6	20.3 20.3 20.3	-10.2 -10.2 -10.2	19.4	12.8		22.6 22.6 22.6	17.7 17.7 17.7	-21.7 -21.7 -21.7	20.3	12.2	-39.9
Mean± S.D.	22.6	33.5		22.6 0	20.3 0		19.4	12.8		22.6 0	17.7 0		20.3	12.2	
t-test				P<0.01						P<0.01					
Sequence of Challenge [(a)]	(1)			(2)			(3)			(4)			(5)		

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm H_2O/1/sec.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

TABLE 18 (Continued)

Cat No. 1478

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

	Control	Cig. Smoke	% Change	Control	Mech. Stim.	% Change	Control	High SO_2	% Change		
Pulmonary Flow Resistance (b)											
	17.4	13.1	-25.8	15.2	77.9	321	23.4	21.3	-6.0		
	17.9	13.6	-22.9	20.1			21.2	18.3	-19.3		
		12.3	-30.3	20.1			23.4	14.3	-36.9		
Mean±	17.7	13.0		18.5	77.9		22.7	18.0			
S.D.	0.4	0.7		2.8			1.3	3.5			
t-test					REFLEX INTACT			Δ N.S.			
Lung Compliance (c)											
	21.4	21.4	0	20.3	17.7	-7.3	16.3	14.6	-14.1		
	21.4	18.5	-13.6	18.5			17.7	14.5	-14.1		
		18.5	-13.6	18.5				14.1	-17.1		
Mean±	21.4	19.5		19.1	17.7		17.0				
S.D.	0			1.0			1.0	14.4			
								0.3			
t-test								Δ N.S.			
Sequence of Challenge (a)		(6)			(7)			(8)			

*Control for 15 minutes preceding challenge.
(a) See Figure.
(b) Pulmonary Flow Resistance, Cm H_2O/1/sec.
(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant (P>0.05)

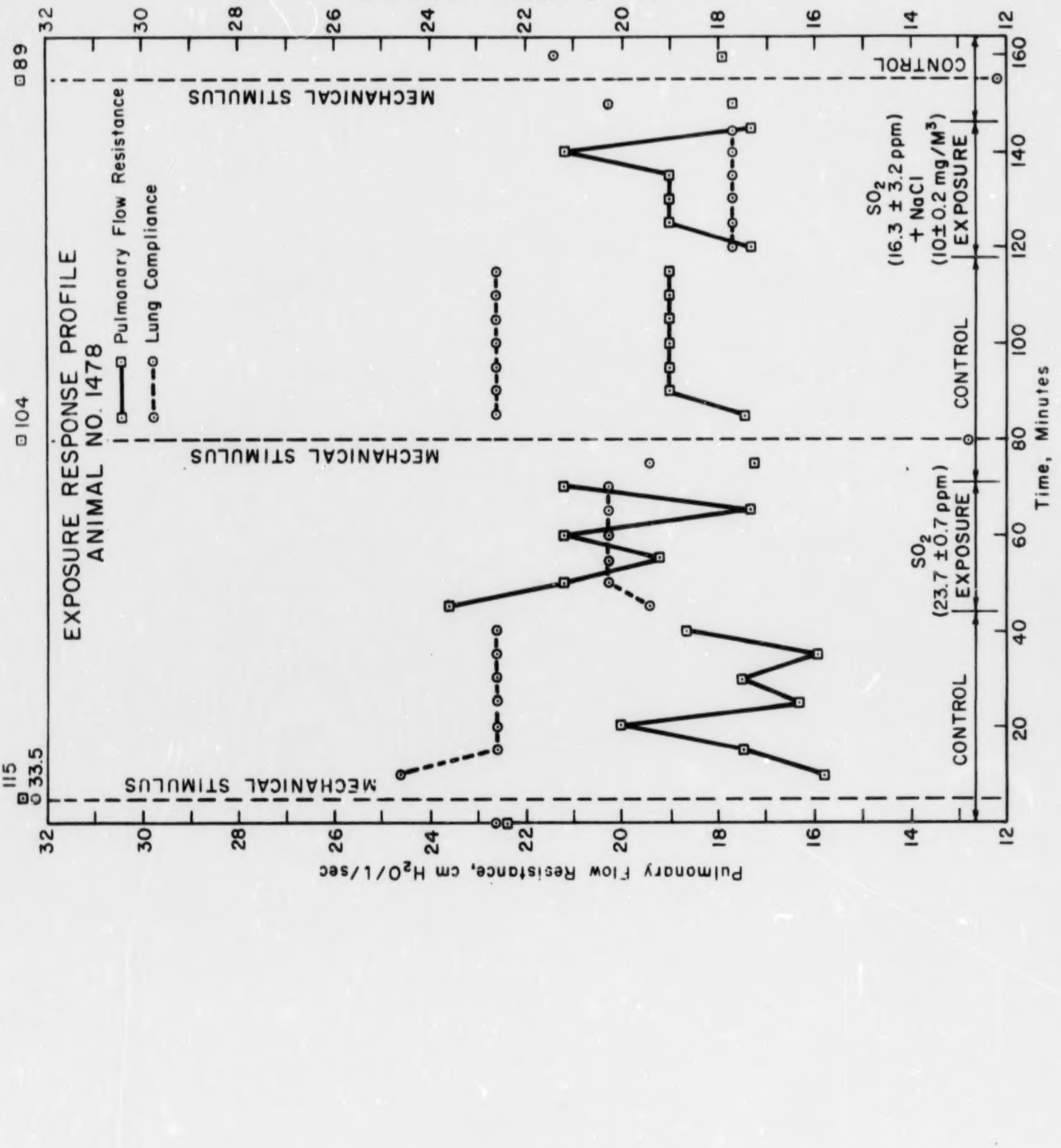

EXPOSURE RESPONSE PROFILE
ANIMAL NO. 1478
Pulmonary Flow Resistance
Lung Compliance
MECHANICAL STIMULUS
MECHANICAL STIMULUS
MECHANICAL STIMULUS
CONTROL
SO2 (23.7 ± 0.7 ppm) EXPOSURE
CONTROL
SO2 (16.3 ± 3.2 ppm) + NaCl (10 ± 0.2 mg/M3) EXPOSURE
CONTROL
115
33.5
104
89
Time, Minutes
20
40
60
80
100
120
140
160
Pulmonary Flow Resistance, cm H2O/l/sec
12
14
16
18
20
22
24
26
28
30
32
Lung Compliance, ml/cm H2O

TABLE 19

Cat No. 32135

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

	Control	Elec. Stim.	% Change	Control	Low SO_2	% Change	Control	Elec. Stim.	% Change	Control	Elec. Stim.	% Change	Control	SO_2+ NaCl	% Change
Pulmonary Flow Resistance [(b)]															
	19	30.7	61.6	11.6	11.8	7.6	11.8	9.9	-8.3	11.2	10.4	-2.8	9.7	13.2	36.1
				9.7	12.5	14.0	9.8			9.8				11.8	21.6
				9.2	12.5	14.0				11.1				12.2	25.8
Mean±	19	30.7		10.2	12.3		10.8	9.9		10.7	10.4		9.7	12.4	
S.D.				1.3	0.4		1.4			0.8				0.7	
		REFLEX INTACT			Δ N.S.			REFLEX QUESTIONABLE			REFLEX QUESTIONABLE			P< 0.05	
Lung Compliance [(c)]															
	13.1	10.2	-22.1	13.6	14.5	18.2	12.7	14.5	2.5	12	13.1	9.2	12	10.5	-12.5
				11.6	14.0	14.1	15.6			12	12	0		9.7	-19.2
				11.6	12.7	13.5				12	12	0		10	-16.7
Mean±	13.1	10.2		12.3	13.7		14.2	14.5		12.0	12.4		12.0	10.1	
S.D.				1.2	0.8		2.1			0	0.6		0	0.4	
t-test					Δ N.S.									P< 0.05	
Sequence of Challenge [(a)]		(1)			(2)			(3)			(4)			(5)	

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm H_2O/1/sec.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

TABLE 20 (Continued)

Cat No. 32135

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

	Control	Elec. Stim.	% Change	Control	NaCl	% Change			
Pulmonary Flow Resistance (b)									
	11.7	14.8	31	11.7	11.3	0			
	11.7			11.7	14.4	27.4			
	10.5			10.5	12.1	7.1			
Mean±	11.3	14.8		11.3	12.6				
S.D.	0.7			0.7	1.6				
t-test		REFLEX QUESTIONABLE			Δ N.S.				
Lung Compliance (c)									
	Control	Elec. Stim.	% Change	Control	NaCl	% Change			
	12.7	11.6	-7.2	12.7	10.7	-14.2			
	12.7			12.7	10.7	-14.2			
	12.0			12.0	10.7	-14.2			
Mean±	12.5	11.6		12.5	10.7				
S.D.	0.4			0.4	0				
t-test					P<0.05				
Sequence of Challenge (a)		(6)			(7)				

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm $H_2O/1/sec$.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

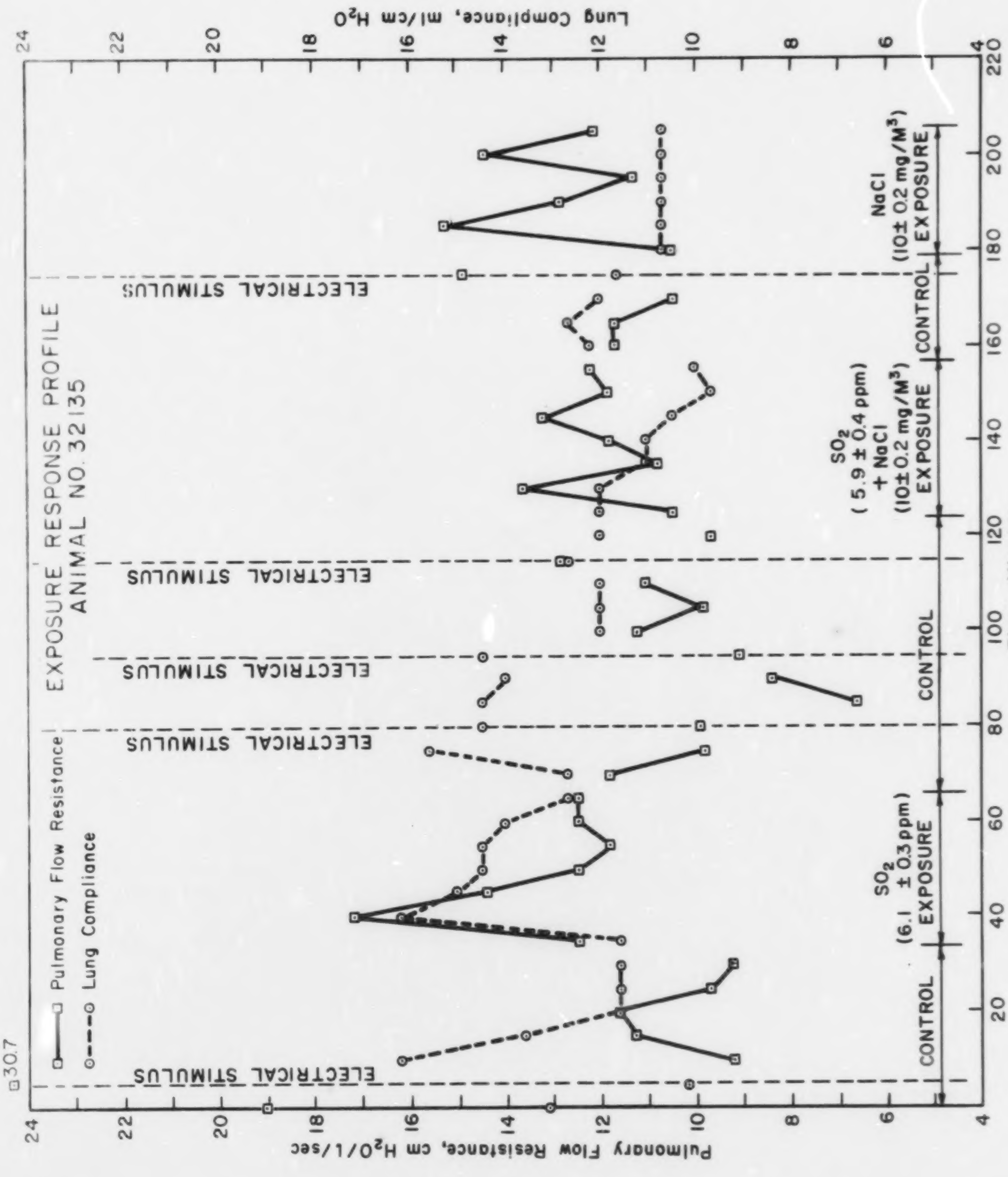

EXPOSURE RESPONSE PROFILE
ANIMAL NO. 32135
Pulmonary Flow Resistance
Lung Compliance
30.7
ELECTRICAL STIMULUS
ELECTRICAL STIMULUS
ELECTRICAL STIMULUS
ELECTRICAL STIMULUS
ELECTRICAL STIMULUS
CONTROL
SO_2 (6.1 ± 0.3 ppm) EXPOSURE
CONTROL
CONTROL
SO_2 (5.9 ± 0.4 ppm) + NaCl (10 ± 0.2 mg/M^3) EXPOSURE
CONTROL
NaCl (10 ± 0.2 mg/M^3) EXPOSURE
Pulmonary Flow Resistance, cm H_2O/L/sec
Lung Compliance, ml/cm H_2O
Time, Minutes
4
6
8
10
12
14
16
18
20
22
24
20
40
60
80
100
120
140
160
180
200
220

TABLE 21

Cat No. 35354

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

Pulmonary Flow Resistance (b)													
	Control	Elec. Stim.	% Change	Control	SO_2	% Change	Control	SO_2+ NaCl	% Change	Control	Elec. Stim.	% Change	
	20.3	51.6	154	21.8	27.9	18.7	19.2	26.4	21.7	18.4	19.6	-10.1	
				25.5	27.9	18.7	21.6	20.5	-5.5	23.0			
				23.2	27.9	18.7	24.4	20.8	-4.1	24.0			
Mean±	20.3	51.6		23.5	27.9		21.7	22.6		21.8	19.6		
S.D.				1.9	0		2.6	3.3		3.0			
t-test	REFLEX INTACT			Δ N.S.			Δ N.S.			REFLEX QUESTIONABLE			
Lung Compliance (c)													
	Control	Elec. Stim.	% Change	Control	SO_2	% Change	Control	SO_2+ NaCl	% Change	Control	Stim.	% Change	
	10.9	10.5	-3.7	9.5	9.5	1.1	10.7	10.0	-6.5	10.5	10.5	1.0	
				9.3	9.5	1.1	10.7	10.0	-6.5	10.1			
				9.3	9.9	5.3	10.7	10.4	-2.8	10.7			
Mean±	10.3	10.5		9.4	9.6		10.7	10.1		10.4	10.5		
S.D.				0.1	0.2		0	0.2		0.3			
t-test				Δ N.S.			Δ N.S.						
Sequence of Challenge (a)	(1)			(2)			(3)			(4)			

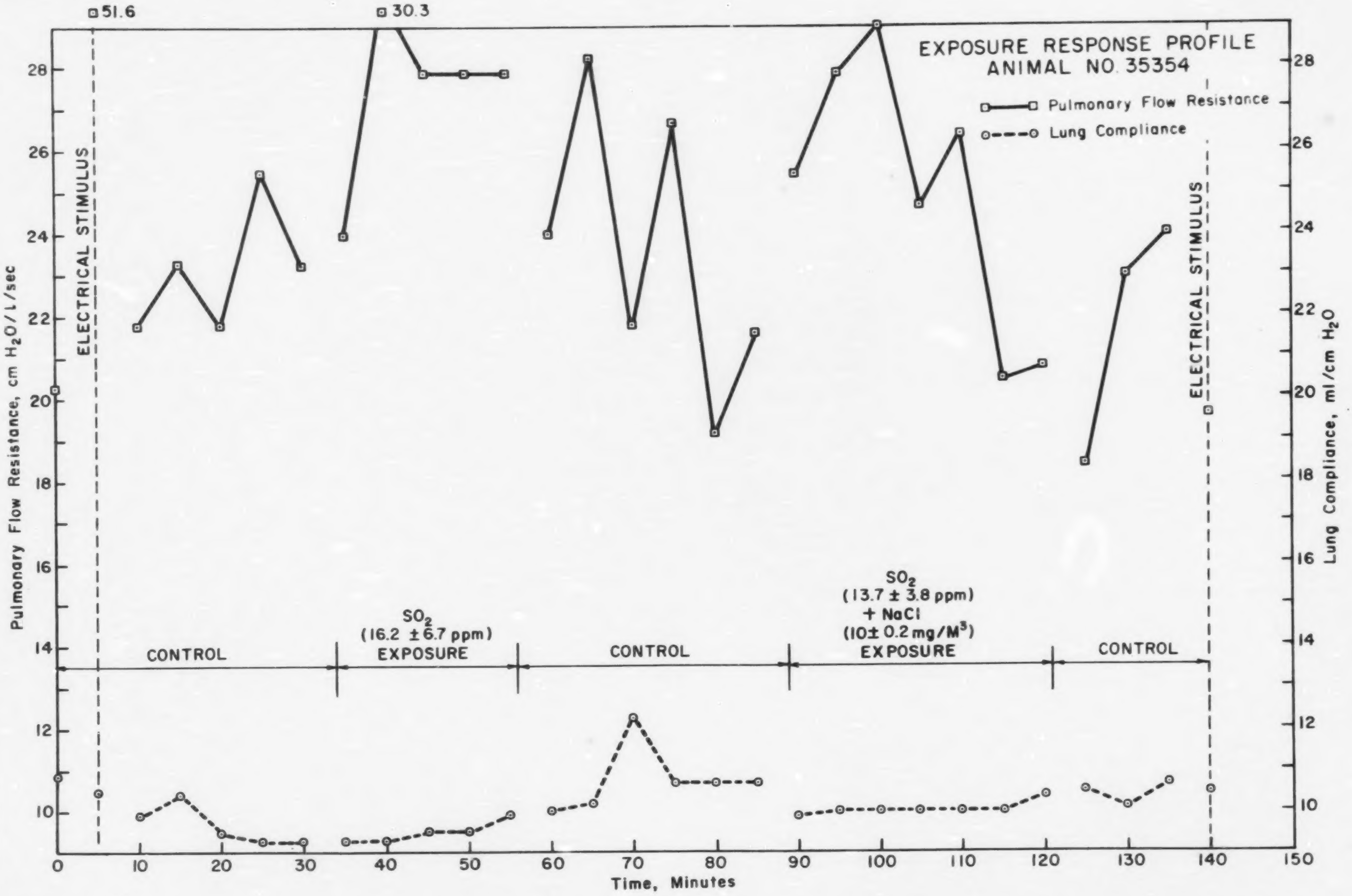
*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm H_2O/1/sec.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)



EXPOSURE RESPONSE PROFILE
ANIMAL NO. 35354

TABLE 22

Cat No. 1807

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

Pulmonary Flow Resistance (b)															
	Control	Mech. Stim.	% Change	Control	High SO_2	% Change	Control	Mech. Stim.	% Change	Control	NaCl	% Change	Control	Mech. Stim.	% Change
	15.4	55.1	+240.1	16.6	9.7	-41.6	12.2	17.0	38.8	10.8	13.7	7.6	12.3	31.8	158
	16.6			16.6	12.3	-25.9	12.3			13.7	12.2	-4.2			
	16.6			16.6	7.1	-57.2				13.7	13.7	7.6			
Mean±	16.2	55.1		16.6	9.7		12.5	17.0		12.7	13.2		12.3	31.8	
S.D.	0.7			0	2.6		0.1			1.7	0.9				
t-test	REFLEX INTACT			P<-0.05			REFLEX QUESTIONABLE			Δ N.S.			REFLEX INTACT		
Lung Compliance (c)															
	Control	Mech. Stim.	% Change	Control	High SO_2	% Change	Control	Mech. Stim.	% Change	Control	NaCl	% Change	Control	Mech. Stim.	% Change
	9.9	5.6	-43.4	9.9	14.2	42.5	9.5	7.7	-42.8	14.2	11.7	-14.4	12.0	10.6	-11.7
	9.9			9.9	14.6	46.5	17.4			13.4	11.4	-16.6			
	9.9			10.1	15.1	51.5				13.4	11.4	-16.6			
Mean±	9.9	5.6		10.0	14.6		13.5	7.7		13.7	11.5		12.0	10.6	
S.D.	0			0.1	0.5		5.6			0.5	0.2				
				P<0.01						P<-0.01					
Sequence of Challenge (a)	(1)			(2)			(3)			(4)			(5)		

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm $H_2O/1/sec$.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

TABLE 22 (Continued)

Cat No. 1807

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

Pulmonary Flow Resistance (b)				
Control				
13.6 16.3 13.7 Mean± 14.5 S.D. 1.5				
Lung Compliance (c)				
Control				
11.4 11.1 11.4 Mean± 11.3 S.D. 0.2				
Sequence of Challenge (a)	(6)			

*Control for 15 minutes preceding challenge.
(a) See Figure.
(b) Pulmonary Flow Resistance, Cm H_2O/1/sec.
(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

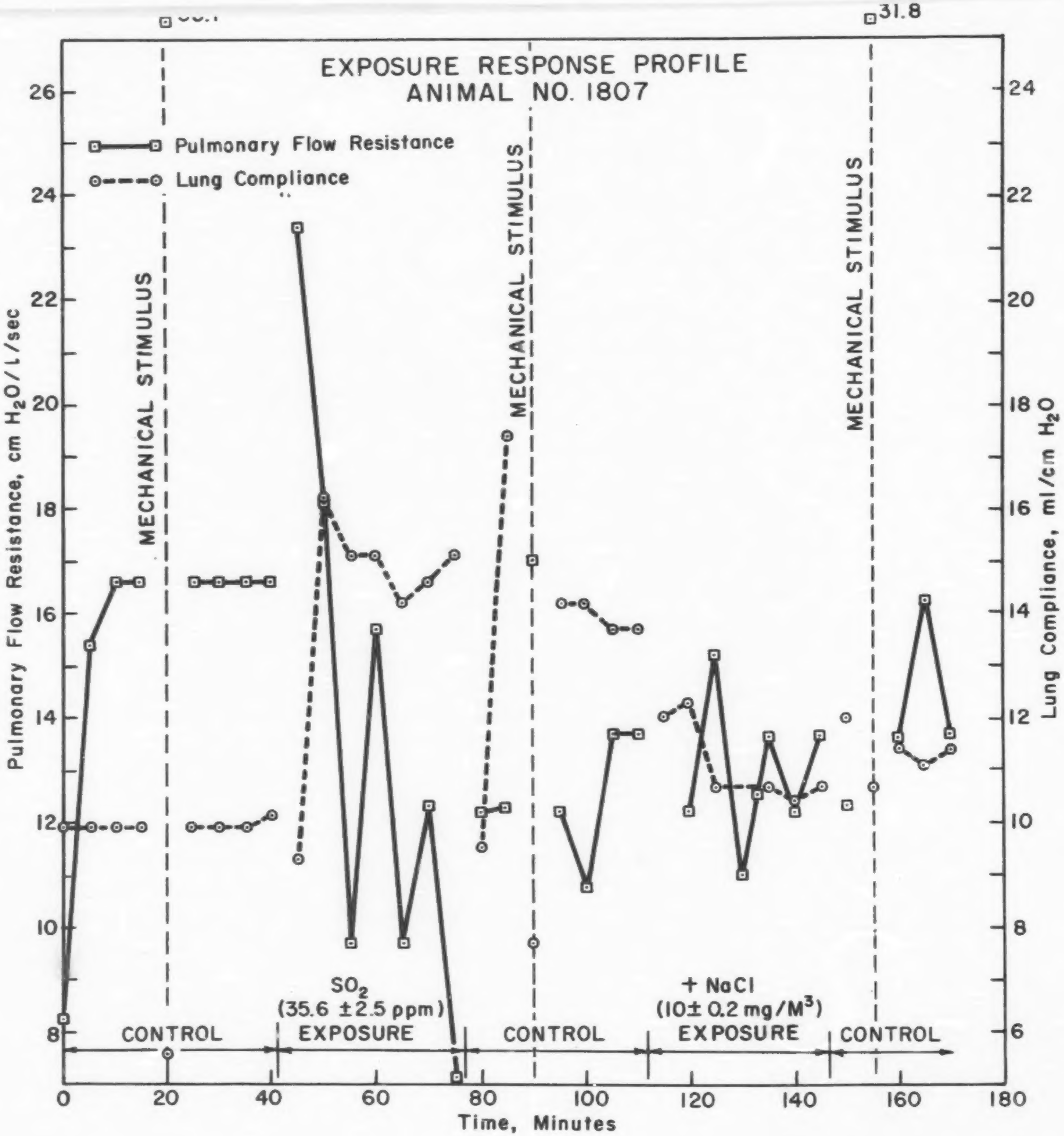

EXPOSURE RESPONSE PROFILE
ANIMAL NO. 1807
Pulmonary Flow Resistance
Lung Compliance
MECHANICAL STIMULUS
MECHANICAL STIMULUS
MECHANICAL STIMULUS
31.8
CONTROL
SO_2 (35.6 ±2.5 ppm) EXPOSURE
CONTROL
+ NaCl (10± 0.2 mg/M^3) EXPOSURE
CONTROL
Pulmonary Flow Resistance, cm H_2O/l/sec
8
10
12
14
16
18
20
22
24
26
Lung Compliance, ml/cm H_2O
6
8
10
12
14
16
18
20
22
24
Time, Minutes
0
20
40
60
80
100
120
140
160
180

TABLE 23

Cat No. 1486

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

	Pulmonary Flow Resistance [b]												
	Control	Mech. Stim.	% Change	Control	SO_2+ NaCl	% Change	Control	Mech. Stim.	% Change	Control	Low SO_2	% Change	Control
	25.6	128	376	29.2	32.2	7.3	28.5	117	302	35.9	24.7	-31.2	26.9
	27.0			31.0	33.8	12.7	29.2				26.9	-25.1	24.2
	27.9			29.8	30.2	0.7					26.4	-26.5	
Mean±	26.9			30.0	32.1		29.1	117		35.9	26.0		25.5
S.D.	1.2			0.9	1.8		0.2				1.2		
t-test	REFLEX INTACT				Δ N.S.			REFLEX INTACT			P< 0.01		
	Lung Compliance [c]												
	Control	Mech. Stim.	% Change	Control	SO_2+ NaCl	% Change	Control	Mech. Stim.	% Change	Control	Low SO_2	% Change	Control
	5.3	3.8	-24.5	5.0	4.5	-10.0	5.3	3.6	-40	8.1	6.2	-23.5	6.3
	4.9			5.0	4.6	-8.0	6.5				6.0	-25.9	6.3
	4.9			5.0	4.6	-8.0					5.6	-30.9	
Mean±	5.0			5.0	4.5		5.9	3.6			5.9		6.3
S.D.	0.2			0.0	0.1		0.8				0.3		
t-test					$P<0.01$						P< 0.01		
Sequence of Challenge[a]		(1)			(2)			(3)			(4)		(5)

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm H_2O/1/sec.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

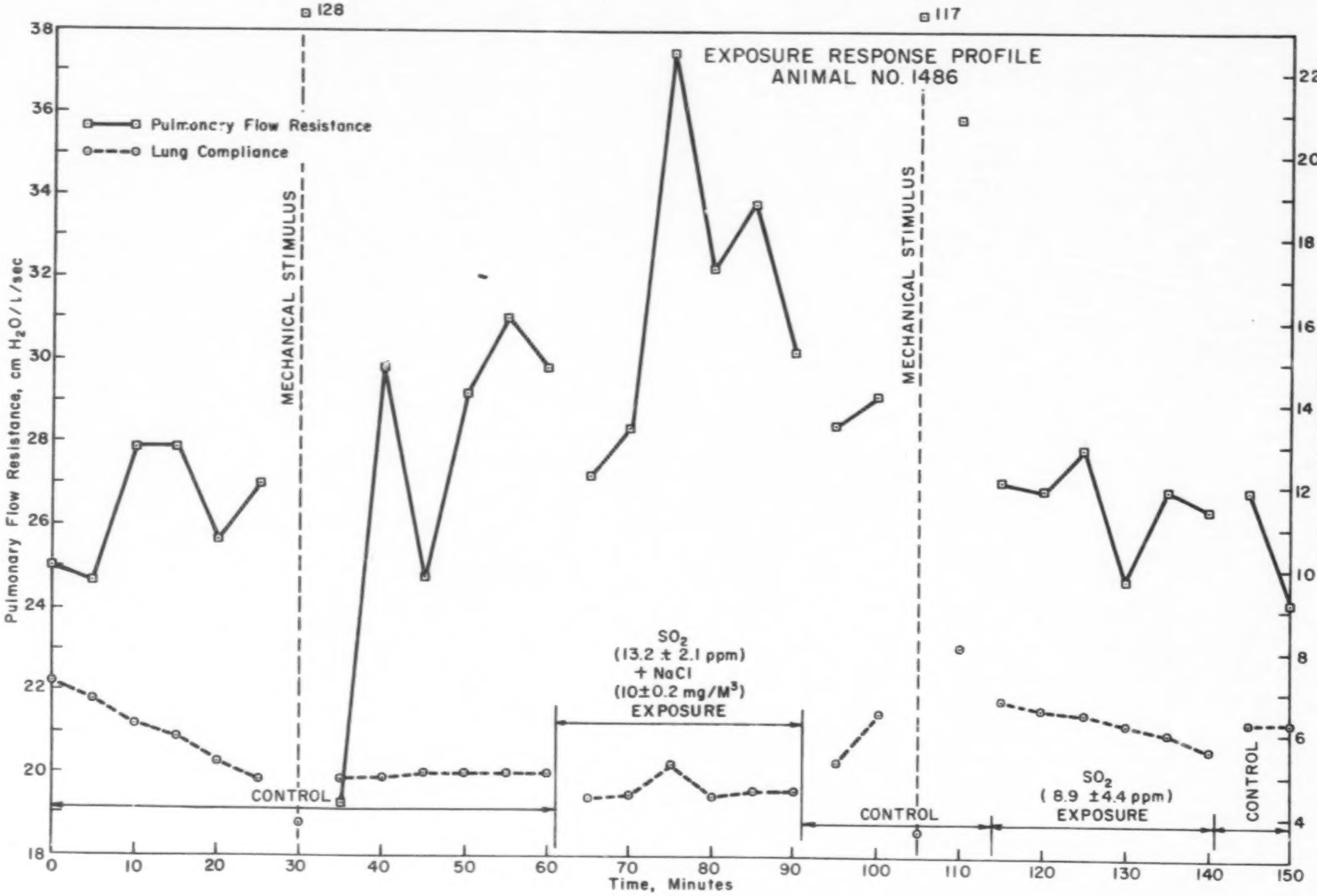

EXPOSURE RESPONSE PROFILE
ANIMAL NO. 1486
Pulmonary Flow Resistance
Lung Compliance
Pulmonary Flow Resistance, cm H_2O/l/sec
Lung Compliance, ml/cm H_2O
Time, Minutes
128
117
MECHANICAL STIMULUS
MECHANICAL STIMULUS
CONTROL
SO_2 (13.2 ± 2.1 ppm) + NaCl (10±0.2 mg/M^3) EXPOSURE
CONTROL
SO_2 (8.9 ±4.4 ppm) EXPOSURE
CONTROL
18
20
22
24
26
28
30
32
34
36
38
4
6
8
10
12
14
16
18
20
22
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150

TABLE 24

Cat No. 1144

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

	Control	Mech. Stim.	Percent Change	Control	Low SO_2	Percent Change	Control	Mech. Stim.	Percent Change	Control	SO_2+ NaCl	Percent Change	Control	Mech. Stim.	Percent Change
Pulmonary Flow Resistance (b)															
	30.2	131	326.7	34.6	41.8	19.5	35.2	99.3	182.1	47.9	45	11.7	43.5	84.7	94.7
	31.2			33.8	40.5	15.8				36.5	45	11.7			
				36.5	40.5	15.8				36.5	45	11.7			
Mean ±	30.7	131		35.0	40.9		35.2	99.3		40.3	45.0		43.5	84.7	
S.D.	0.7			1.4	0.8					6.6	0				
t-test	REFLEX INTACT			$P<0.01$			REFLEX INTACT			Δ N.S.			REFLEX INTACT		
Lung Compliance (c)															
	Control	Mech. Stim.	Percent Change	Control	Low SO_2	Percent Change	Control	Mech. Stim.	Percent Change	Control	SO_2+ NaCl	Percent Change	Control	Mech. Stim.	Percent Change
	5.8	4.2	-28.9	6.4	6.7	3.1	7.8	4.0	-48.7	6.4	5.9	-6.3	6.4	4.4	-31.3
	6.0			6.6	6.4	-1.5				6.3	5.9	-6.3			
				6.6	6.4	-1.5				6.2	5.9	-6.3			
Mean ±	5.9	4.2		6.5	6.5		7.8	4.0		6.3	5.9		6.4	4.4	
	0.1			0.1	0.2					0.1	0				
t-test				Δ N.S.						$P<0.05$					
Sequence of Challenge (a)															

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm H_2O/l/sec.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

TABLE 24 (Continued)

Cat No. 1144

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

Pulmonary Flow Resistance (b)							
	Control	High SO_2	Percent Change				
	40.5	55.3	46.2				
	36.5	47.1	24.5				
	36.5	45	18.9				
Mean±	37.8	49.1					
S.D.	2.3	5.4					
t-test		P< 0.05					
Lung Compliance (c)							
	Control	High SO_2	Percent Change				
	5.8	6.0	2.3				
	5.9	5.9	0.6				
	5.9	5.9	0.6				
Mean±	5.8	5.9					
S.D.	0.1	0.1					
t-test		Δ N.S.					
Sequence of Challenge (a)							

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm H_2O/l/sec.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

TABLE 25

Cat No. 2393

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

	Control	Low SO_2	Percent Change	Control	High SO_2	Percent Change	Control		
Pulmonary Flow Resistance (b)									
	47.4 39.6 41.1	31.8 34.9 36.4	-25.5 -18.3 -14.8	45.9 44.2 41.1	45.9 49.9 47.3	4.8 11.9 8.2	48.9		
Mean± S.D.	42.7 4.1	34.4 2.3		43.7 2.4	47.3 1.6		48.9		
t-test		P<0.05			ΔN.S.				
Lung Compliance (c)									
	7.8 9.2 8.8	8.2 8.7 8.4	-4.7 1.2 -2.3	8.6 8.7 9.0	9.7 8.6 9.5	-0.8 -1.9 8.4	9.5		
Mean± S.D.	8.6 0.7	8.4 0.3		8.8 0.2	8.9 0.5		9.5		
t-test		Δ N.S.			Δ N.S.				
Sequence of Challenge (a)									

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm H_2O/1/sec.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant (P>0.05)

TABLE 26

Cat No. 1988

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

Pulmonary Flow Resistance (b)

	Control	Mech. Stim.	Percent Change	Control	High SO_2	Percent Change	Control	Mech. Stim.	Percent Change	Control	NaCl	Percent Change	Control	Mech. Stim.	Percent Change
	64.2	130.5	112.0	53.1	31.8	-39.4	27.7	73.7	166.1	22.1	18.2	-33.2	22.7	49.3	117.2
	58.9			51.1	35.6	-32.1				29.8	18.2	-33.2			
				53.1	31.8	-39.4				29.8	24.0	-11.9			
Mean±	61.6	130.5		52.4	33.1		27.7	73.7		27.2	20.1		22.7	49.3	
S.D.	3.7			1.2	2.2					4.4	3.3				
t-test	REFLEX INTACT			P< 0.01			REFLEX INTACT			Δ N.S.			REFLEX INTACT		

Lung Compliance (c)

	Control	Mech. Stim.	Percent Change	Control	High SO_2	Percent Change	Control	Mech. Stim.	Percent Change	Control	NaCl	Percent Change	Control	Mech. Stim.	Percent Change
	3.9	3.3	-15.4	4.3	5.2	20.9	6.1	3.3	-45.9	7.6	7.6	2.7	7.4	4.3	-41.9
	3.9			4.3	5.4	25.6				7.4	7.2	-2.7			
				4.3	8.4	95.3				7.2	7.2	-2.7			
Mean±	3.9	3.3		4.3	6.3		6.1	3.3		7.4	7.3		7.4	4.3	
	0.0			0.0	1.8					0.2	0.2				
t-test				Δ N.S.						Δ N.S.					
Sequence of Challenge(a)															

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm $H_2O/l/sec$.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

TABLE 26 (Continued)

Cat No. 1988

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

	Control	SO_2+ NaCl	Percent Change	Control	Mech. Stim	Percent Change	Control	SO_2	Percent Change	Control	Mech. Stim.	Percent Change	
Pulmonary Flow Resistance [(b)]													
	27.9	27.8	-2.1	24.7	33.1	34.0	26.2	26.2	-1.9	29.8	97.6	227.5	
	29.5	27.8	-2.1				27.7	30.7	15.0				
	27.8	31.2	9.9				26.2	31.8	19.1				
Mean±	28.4	28.9		24.7	33.1		26.7	29.6		29.8	97.6		
S.D.	1.0	2.0					0.9	3.0					
t-test		ΔN.S.			REFLEX QUESTIONABLE			Δ N.S.			REFLEX INTACT		
Lung Compliance [(c)]													
	Control	SO_2+ NaCl	Percent Change	Control	Mech. Stim.	Percent Change	Control	SO_2	Percent Change	Control	Mech. Stim.	Percent Change	
	7.4	5.4	-22.9	5.9	5.4	-8.5	5.4	4.9	-10.9	5.7	4.3	-24.6	
	7.0	5.4	-22.9				5.6	4.9	-10.9				
	6.6	5.2	-25.7				5.6	5.0	- 9.1				
Mean±	7.0	5.3		5.9	5.4		5.5	4.9		5.7	4.3		
S.D.	0.4	0.1					0.1	0.1					
t-test		P< 0.01						0.01					
Sequence of Challenge [(a)]													

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm H_2O/l/sec.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

TABLE 27

Cat No. 1801

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

	Pulmonary Flow Resistance (b)														
	Control	Mech. Stim.	% Change	Control	High SO_2	% Change	Control	Mech. Stim.	% Change	Control	NaCl	% Change	Control	Mech. Stim.	% Change
	23.3	33.7	43.7	18.1	18.1	-16.8	23.6	45	90.7	22.0	45.8	93.8	46.6	89.6	92.3
	23.6			23.6	25.3	16.2				23.6	56.4	133.6			
				23.6	22.0	1.1				25.3	61.4	159.8			
Mean±	23.5	33.7		21.8	21.8		23.6	45.0		23.6	54.5		46.6	89.6	
S.D.	0.2			3.2	3.6					1.7	8.0				
	REFLEX INTACT			Δ N.S.			REFLEX INTACT			P<0.05			REFLEX INTACT		
	Lung Compliance (c)														
	Control	Mech. Stim.	Change	Control	High SO_2	% Change	Control	Mech. Stim.	% Change	Control	NaCl	% Change	Control	Mech. Stim.	% Change
	6.3	4.9	-21.6	5.2	6.0	12.5	6.0	5.7	-5.0	5.7	4.7	-15.6	4.8	4.8	0
	6.2			5.4	5.7	6.9				5.6	4.6	-17.4			
				5.4	5.4	1.3				5.4	4.5	-19.2			
Mean±	6.2	4.9		5.3	5.7		6.0	5.7		5.6	4.6		4.8	4.8	
S.D.	0.1			0.1	0.3					0.2	0.1				
				Δ N.S.						P<0.01					
Sequence of Challenge (a)	(1)			(2)			(3)			(4)			(5)		

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm H_2O/1/sec.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

TABLE 27 (Continued)

Cat No. 1801

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

	Control	SO_2+ NaCl	% Change	Control	Mech. Stim.	% Change	Control	SO_2	% Change	Control	Mech. Stim.	% Change	
Pulmonary Flow Resistance (b)													
	23.6	25.3	-2.7	25.3	57.0	125.3	22.0	25.3	15.0	21.4	64.5	201.4	
	23.6	23.9	-8.1				22.0	28.6	30.0				
	30.8	21.0	-19.2				22.0	32.6	48.2				
Mean±	26.0	23.4		25.3	57.0		22.0	23.8		21.4	64.5		
S.D.	4.2	2.2					0.1	3.7					
	Δ N.S.			REFLEX INTACT			Δ N.S.			REFLEX INTACT			
Lung Compliance (c)													
	Control	SO_2+ NaCl	% Change	Control	Mech. Stim.	% Change	Control	SO_2	% Change	Control	Mech. Stim.	% Change	
	5.9	4.3	-20.4	5.1	5.2	2.0	5.0	4.2	-12.5	4.9	4.9	0	
	5.6	4.3	-20.4				4.7	4.0	-16.7				
	4.7	4.3	-20.4				4.7	4.2	-12.5				
Mean±	5.4	4.3		5.1	5.2		4.9	4.1		4.9	4.9		
	0.6	0					0.2	0.1					
	Δ N.S.						$P<0.01$						
Sequence of Challenge (a)	(6)			(7)			(8)			(9)			

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm H_2O/1/sec.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

TABLE 28

Cat No. 1781

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

	Pulmonary Flow Resistance (b)										
	Control	Mech. Stim.	% Change	Control	High SO_2	% Change	Control	Mech. Stim.	% Change		
	26.1	80.6	177.9	17.4	9.6	-42.1	16.1	44.4	175.8		
	31.9			16.6	18.7	12.9					
				15.7	18.0	8.7					
Mean±	29.0	80.6		16.6	15.4		16.1	44.4			
S.D.	4.1			0.9	5.1						
t-test	REFLEX INTACT			Δ N.S.			REFLEX INTACT				
	Lung Compliance (c)										
	Control	Mech. Stim.	% Change	Control	High SO_2	% Change	Control	Mech. Stim.	% Change		
	6.7	6.0	-14.9	7.3	6.6	-8.8	6.7	5.6	-16.4		
	7.4			7.3	6.6	-8.8					
				7.1	6.7	-7.4					
Mean±	7.1	6.0		7.2	6.6		6.7	5.6			
	0.5			0.1	0.1						
t-test				$P<0.01$							
Sequence of Challenge (a)	(1)			(2)			(3)				

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm H_2O/1/sec.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

TABLE 29

Cat No. 2206

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

	Control	SO_2 Both Sites	Percent Change	Control	SO_2 Mouth	Percent Change	Control	SO_2 Trachea	Percent Change	Control	
Pulmonary Flow Resistance (b)											
	44.6	37.3	-16.4	44.6	34.9	-21.7	44.6	32.5	-27.1	42.2	
	44.6	42.2	-5.4	44.6	37.3	-16.4	44.6	27.3	-38.8		
	44.6	42.2	-5.4	44.6	34.1	-23.5	44.6	30.0	-32.7		
Mean±	44.6	40.6		44.6	35.4		44.6	29.9		42.2	
S.D.	0.0	2.8		0.0	1.7		0.0	2.6			
t-test		Δ N.S.			P< 0.05			P< 0.05			
Lung Compliance (c)											
	5.3	4.6	-16.4	5.2	5.8	8.8	5.6	5.0	-10.7	5.0	
	5.6	4.5	-18.2	5.5	5.3	-0.6	5.6	4.8	-14.3		
	5.6	5.0	- 9.1	5.3	5.6	5.0	5.6	5.0	-10.7		
Mean±	5.5	4.7		5.3	5.6		5.6	5.0		5.0	
S.D.	0.2	0.3		0.2	0.3		0.0	0.1			
t-test		P<0.01			Δ N.S.			P< 0.01			
Sequence of Challenge (a)											

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm $H_2O/1/sec.$

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

TABLE 30

Cat No. 53869

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

	Pulmonary Flow Resistance [b]										
	Control	SO_2 Both Sites	Percent Change	Control	SO_2 Mouth	Percent Change	Control	SO_2 Trachea	Percent Change	Control	
	9.6	13.5	44.6	9.6	13.6	41.7	10.9	13.5	23.9	12.3	
	8.8	14.2	52.1	9.6	11.8	22.9	10.9	14.2	30.3		
	9.6	13.5	44.6	9.6	12.0	25.0	10.9	12.9	18.3		
Mean±	9.3	13.7		9.6	12.5		10.9	13.5		12.3	
S.D.	0.5	0.4		0.0	1.0		0.0	0.7			
t-test		$P < 0.01$			$P < 0.05$			$P < 0.05$			
	Lung Compliance [c]										
	Control	SO_2 Both Sites	Percent Change	Control	SO_2 Mouth	Percent Change	Control	SO_2 Trachea	Percent Change	Control	
	22.7	19.4	-14.5	22.7	18.1	-20.3	19.4	15.9	-19.2	18.7	
	22.7	19.4	-14.5	22.7	19.4	-14.5	19.4	16.4	-16.6		
	22.7	20.2	-11.0	22.7	18.7	-17.6	20.2	15.9	-19.2		
Mean±	22.7	19.7		22.7	18.7		19.7	16.1		18.7	
	0.0	0.5		0.0	0.7		0.5	0.3			
t-test		$P < 0.01$			$P < 0.01$			$P < 0.01$			
Sequence of Challenge [a]											

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm H_2O/l/sec.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)

TABLE 31

Cat No. 2984

RESPONSE TO VARIOUS STIMULI EXPRESSED AS PERCENT CHANGE RELATIVE TO CONTROL VALUES*

Pulmonary Flow Resistance (b)											
	Control	SO_2 Trachea	Percent Change	Control	SO_2 Mouth	Percent Change	Control	SO_2 Both Sites	Percent Change	Control	
	42.2	25.7	-39.1	42.2	39.4	-6.6	42.2	23.0	-45.5	36.7	
	42.2	23.0	-45.5	42.2	42.2	0	42.2	21.9	-48.1		
	42.2	23.0	-45.5	42.2	42.2	0	42.2	25.3	-40.0		
Mean±	42.2	23.9		42.2	41.3		42.2	23.4		36.7	
S.D.	0.0	1.6		0.0	1.6		0.0	1.7			
t-test	P< 0.01			Δ N.S.			P< 0.01				
Lung Compliance (c)											
	Control	SO_2 Trachea	Percent Change	Control	SO_2 Mouth	Percent Change	Control	SO_2 Both Sites	Percent Change	Control	
	5.3	5.6	0.6	5.3	6.7	14.9	6.0	5.8	-8.9	8.2	
	5.4	5.6	0.6	6.4	6.9	18.3	6.4	5.6	-12.0		
	6.0	5.6	0.6	5.8	6.7	14.9	6.7	5.8	-8.9		
Mean±	5.6	5.6		5.8	6.8		6.4	5.7		8.2	
	0.4	0.0		0.6	0.1		0.4	0.1			
t-test	Δ N.S.			Δ N.S.			Δ N.S.				
Sequence of Challenge (a)											

*Control for 15 minutes preceding challenge.

(a) See Figure.

(b) Pulmonary Flow Resistance, Cm H_2O/1/sec.

(c) Lung Compliance, ml/cm H_2O.

Δ N.S. = Difference between means not sigificant ($P>0.05$)